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ANNALS OF INTERNAL MEDICINE

VOLUME 10 JUNE, 1937 NUMBER 12

ADDRESS AT THE ANNUAL CONVOCATION OF THE AMERICAN COLLEGE OF PHYSICIANS *

By the President of the College, ERNEST B. BRADLEY, F.A.C.P.,
Lexington, Kentucky

IT seems impossible that you should have chosen me, even for one year, to be the President of the American College of Physicians. No greater distinction could come to any man engaged in the practice of Internal Medicine. To me the honor is almost overpowering. All preceding presidents, with possibly one exception, have been teachers and professors of medicine, and even the one exception was a nationally known internist, who came from a great medical center. I could not claim such qualifications. To explain my selection I decided that your Board of Regents and the Nominating Committee felt it was time to show real democracy—to recognize one of that numerous class, who have not had medical honors heaped upon them.

Having been a member of your Board of Governors for a number of years and at that time its Chairman, I took the honor as one bestowed, not upon me personally, but as a recognition by the Board of Regents of the high regard in which your Board of Governors is held. Therefore, as a former Governor, I thank you for them.

Former Presidents, the list of whom includes many of the most eminent internists in the United States and Canada, have delivered addresses which have shown remarkable understanding of modern medical problems. They have explained the ramifications of medical trends and have given sound advice to the members of this organization. Some have gone quite deeply into the discussion of modern problems affecting doctors, " socialized medicine," " state medicine," " social security," etc. These economic questions are very important, but they are also very involved. It might be advisable at our next meeting to devote a whole afternoon or evening to such questions alone. I must confess that I feel incapable of dealing with them adequately, nor would I venture to discuss the various medical problems that are agitat-

* Presented at the St. Louis meeting of the American College of Physicians, April 19, 1937.

ing us today, so instead of a Presidential Address, I will try to review briefly the progress of the College during my term of office and to point out to you certain aspects that have impressed me as President. This year has taught me in what great esteem our College is held by other organizations, both lay and medical, and to appreciate the opportunities which this body has for the betterment of medical practice in America.

Except for the preparation of the program of the General Sessions, your President is more or less of a figure-head. It is for this reason, no doubt, that the College has done just as well during the past year as in any preceding one. In fact, its achievements may have been somewhat above the average. When I say that the President is a figure-head, I do not mean this too literally. He has a great deal to do. The major credit, however, should go to the Board of Regents and to the Board of Governors, who individually and through their committees give unsparingly of their time and energy. It is this coöperation that makes the duties of the President a pleasure rather than a task.

In summing up the activities of the College, attention is called first to probably our most important department—the business office. It is here that the Executive-Secretary, Mr. E. R. Loveland, with his clerical assistants take care promptly and efficiently of a vast amount of work. This office is perfectly organized and all records are kept in such a way as to be instantly available when needed. There are multitudinous details connected with applications for membership. Every candidate is investigated most carefully with respect to his qualifications, professional, social and ethical. Cards are sent to all of our members who live anywhere near the residence of the candidate, or, if he has recently changed his address, to all members near his former location. All this information is tabulated so well that the work of the Committee on Credentials is lightened as much as possible. In addition to routine business, collection of dues, etc., there is the preparation and publication of the Directory every two years. And every year there is an immense amount of work connected with the Annual Sessions. Obtaining and arranging the commercial exhibits and preparing the program are but a few of the duties that must be performed. It would be impossible for me to enumerate the many activities of our business office, but all are handled promptly, efficiently and with dignity.

In connection with the work of the business office I have mentioned the preparation and publication every other year of the Directory of our members. This is a most valuable book of reference. The last edition and supplement contains, geographically as well as alphabetically arranged, the names of 3600 physicians engaged in internal medicine and allied specialties. With its biographical data it is invaluable in referring patients to other physicians in distant cities. It is becoming more and more appreciated as a most important " Who's Who " in Internal Medicine.

While we are mentioning assets of which we are proud, your attention is called to the Journal which the College owns and controls. Under the

able Editorship of Dr. Maurice Pincoffs, the ANNALS OF INTERNAL MEDICINE has shown a growth that is very gratifying. Each year it has increased in size and importance. The current volume for the twelve months will contain at the present rate almost two thousand pages of scientific reading matter, book reviews, editorials and College news. The scientific articles are not published in a haphazard way, but are chosen carefully by the Editorial Board and may be said to represent the best literature devoted entirely to internal medicine in America. There is also cause for satisfaction in knowing that the Annals is now a financial success and is more than self-supporting. In fact, last year it earned a very substantial sum.

These annual clinical sessions affording a renewal of old friendships and an interchange of medical ideas have come to be regarded by those engaged in the practice of Internal Medicine as the outstanding event of the year. Much of the success of this meeting is due to your General Chairman, Dr. David P. Barr. Together with his associates on the various committees, he has worked long and faithfully to formulate the program which we are enjoying this week. The Clinics at the Hospitals are an inspiration to us all, and we shall not soon forget the hospitality that has been extended to us here in St. Louis. These people from Missouri do not "Have to be shown" how to make us feel at home. We hope that at some future time they will be willing to let us come back again.

Two projects of importance to the College had their culmination during the past year, both of them having been instigated during the year preceding. I refer, first to the organization of the American Board of Internal Medicine, and second, to the purchase of a permanent headquarters.

Initiated by the American College of Physicians, and with the coöperation of the Section on Medicine of the American Medical Association, the American Board of Internal Medicine completed its organization in June 1936 and is now actively functioning. The purpose of this Board is briefly, the certification of specialists in the field of internal medicine. The growth of specialism has called into action many similar Boards of Certification. There are now eleven such boards. They are, in the order of their establishment, the American Boards of, Ophthalmology, Otolaryngology, Obstetrics and Gynecology, Dermatology and Syphilology, Psychiatry and Neurology, Radiology, Orthopedic Surgery, Urology, Internal Medicine, and Pathology. The American Board of Surgery has completed its preliminary steps and is almost ready to function.

The plan of certifying specialists has been one of the developments of modern medicine that has resulted from the enormous growth of specialism itself. Since one could be listed as a specialist by merely claiming to be a specialist, there seemed to be no proper way to distinguish between the qualified and the unqualified. Of course, in many cases, such certification is wholly superfluous. Many specialists by reason of long and successful practice, by their hospital and medical school connections, or by the regard in which they are held by members of the medical profession familiar with

their work, will gain nothing by being certified in any particular specialty. Dr. George H. Meeker, Dean of the Graduate School of Medicine of the University of Pennsylvania has called this " casual " certification, whereas, the evolutionary tendencies in the whole medical field he says are an abandonment of the " casual " for the " systematic." It is this tendency to be more systematic that has caused the growth of these boards of certification. It is evident that certification of internists will result in changes in postgraduate work to provide for more systematic preparation for this specialty. In just what way this will be done is somewhat uncertain. However, it will result probably in a longer training in internal medicine during the years of hospital residence, with more hospitals of approved class offering residencies in medicine. Other changes will no doubt come about, the nature of which cannot be definitely foreseen at this time. In the long run it would seem that certification must result in better preparation before specialism is attempted.

Certain constitutional amendments were proposed at the December meeting of the Board of Regents and have been published in the ANNALS. They would have caused very drastic changes in the selection of new members. The first change was in Article IV, which states that " Fellows shall be members of the medical profession, engaged as practitioners, teachers or research workers in Internal Medicine or in an allied specialty, etc." It was proposed to leave out the phrase, " or in an allied specialty," thus restricting future membership to those engaged in Internal Medicine alone. It was also proposed to make the successful passage of the examination for certification a pre-requisite for Associateship. These changes if adopted, while in no way affecting our present membership, would have influenced materially the future selection of Associates and Fellows. At the meeting of the Board of Regents last Sunday it was decided not to take up consideration of these amendments at this time.

It is apparent that Fellowship in the College will mean much more than mere Certification, which is only one qualification that must be met, just as it is necessary now that the candidate be a graduate of an approved medical school and must hold membership in his county, state and national medical organizations. These are preliminary requirements. Many other qualifications for Fellowship are now considered by the Committee on Credentials, and as time goes on Fellowship will become more difficult and therefore more desirable than in the past.

Two years ago it seemed apparent to the Officers and Regents of our College that a Board for the Certification of Internists would be formed, and it was felt that if such were the case the American College of Physicians should exercise control over it. Since the American Board of Ophthalmology was formed twenty-four years ago and eight other boards were organized prior to the American Board of Internal Medicine, it must be evident that this procedure was not entered into hastily. The personnel of the American Board of Internal Medicine is a sufficient guarantee of its

successful administration. The College owes a great debt to the Chairman and members of this Board for the time and energy which they have spent in this very complicated organization. The Chairman, Dr. Walter L. Bierring, will discuss more fully the workings of this Board at the General Sessions.

The other most interesting achievement of the College during the past year was the purchase of a building in Philadelphia as a permanent home. Encouraged by my predecessor, Dr. James Alexander Miller, the pioneer work on this project was done by Dr. Alfred Stengel prior to our meeting in Detroit last year. Their arguments convinced the Boards of Regents and Governors that the College should own a suitable headquarters building. It no longer seemed appropriate that an organization of our size and importance should occupy rented rooms in an office building. Accordingly, a Committee on College Headquarters was appointed, which after much investigation, advised the purchase of a fine old residence in Philadelphia. This purchase was consummated during the past summer, a few necessary alterations were made and the house was furnished in time for the December meeting of the Board of Regents. The thanks of the College for the selection of the property and for the successful completion of this project should be tendered to this committee, of which Dr. O. H. Perry Pepper was Chairman. Fortunately for us, large city houses of this sort are not in great demand, so that the College was able to acquire a very handsome and expensive property at very little more than the value of the lot upon which it stands. It is situated on the corner of Pine and Forty-Second Streets in Philadelphia in a neighborhood that apparently will not soon deteriorate. The house is a three-story brick residence, dignified in appearance, and is surrounded by a large yard with beautiful planting. The whole property is enclosed by a high iron fence which adds much to its appearance. The advantages of this acquisition are that the executive offices now have abundant space, there are rooms for the meetings of the Board of Regents and their committees, further expansion is provided for when it becomes necessary, and the College has a home of its own of which I am sure you will be proud. All members are urged to visit the new headquarters when in Philadelphia.

One of the encouraging features of the past year has been the increased interest shown in Life Memberships. As you know, the revenue from this source goes into the endowment fund, the income from which is used solely to further the scientific purposes of the College. In the year just closed 18 Fellows have shown concretely that they appreciate this aim of the College. We now have a total of 79 Life Members and about $62,000.00 in this fund.

Numerically, the membership of the College has shown a healthy growth during the year. One hundred and seventy-two have been elected to Fellowship and 276 to Associateship. On the roster of the College at the present time there are 2 Masters, 2684 Fellows and 998 Associates, a total of 3684.

This is a large number and results in such a big attendance at these Annual Sessions that only the largest cities can adequately care for them. However, with the standards for membership being constantly made more rigid, the growth of the College will necessarily be much slower from this time forward, and from a practical standpoint this is not an unmixed evil. The meetings would lose much if they should have to be divided into Regional Assemblies, as is done by another of our national societies.

Detracting in no way from these Annual Sessions have been the state meetings which have shown a remarkable increase in the past two years due to the efforts of our Governors. These state meetings have been more or less social. Some have been held at the time and place of the meeting of the State Medical Society, while others have convened at some central city with or without a scientific program. It has been my good fortune during the past year to attend several of these state gatherings, and at all of them, those in attendance seemed enthusiastic and voted to continue these meetings annually.

After discussing the growth of the College, it is fitting that we now take account of our losses since our last meeting. For failure to pay dues or by resignation we have lost only 10 Fellows and 10 Associates. Death, however, has not been so kind. Two Masters, 52 Fellows and 4 Associates have passed to the "great beyond." Included in this list were some of our most active and distinguished members. Time will permit me to refer to only a few—Henry F. Stoll and Ernest E. Laubaugh, Governors for the States of Connecticut and Idaho respectively, and Luther F. Warren of Brooklyn, a member of the Board of Regents, were actively engaged in the affairs of the College and will be sorely missed. W. McKim Marriott and Henry S. Plummer were former members of the Board of Regents. Both of these men were known personally or by reputation to all of you. Dr. Marriott, as you know, had recently removed from this city to San Francisco. Dr. Plummer's work at the Mayo Clinic is equally well-known to you. It would be futile for me to enumerate the professional attainments of these eminent physicians. Their work is familiar to the whole medical world.

We mourn also tonight three past presidents, James M. Anders, Harlow Brooks and Frank Smithies. James M. Anders, called the "Nestor of the Philadelphia Medical Profession," "A Gentleman of the Old School," was President of the College in 1922 to 1923 and was the first to be honored with the title of "Master of the American College of Physicians." He was known to all internists in America, and was the author of many medical works. He maintained a lively interest in this society until the time of his death.

Harlow Brooks of New York, was President for the two years succeeding Dr. Anders, 1923 to 1925 and was a member of the Board of Regents for a number of years. He became a Fellow in 1916 at the first regular

meeting of the College and also served as Governor of the College for New York from 1929 to 1931. He has been called the "Doctor's Doctor," had a nation-wide reputation as a diagnostician and was widely sought as a consultant. He was loved by all who knew him well.

Frank Smithies, whose death occurred rather suddenly early in February, deserves especial mention. If it had not been for Frank Smithies there might not have been an American College of Physicians; at any rate, he had much to do with its formation. During its early years *he* was the College. He arranged the places of meeting, made out the programs and carried on practically all the business of the College. He was the founder of our Journal. He was Secretary-General from 1922 to 1926 and President 1927 to 1928. In recognition of his work he was made a "Master." Frank Smithies had great personality, he possessed an almost unbelievable capacity for hard work, which in spite of physical handicaps enabled him to win distinction and many honors in the field of American Medicine. In the passing of James M. Anders, Harlow Brooks and Frank Smithies, the College has lost three of its pioneers, who served it in its infancy.

The College is an infant no longer. This year marks the twenty-first Annual Sessions, so that now it may be said to be grown to manhood, and like a young man, it is strong, virile, optimistic and progressive. During these twenty-one years it has gradually attained all the objectives for which these pioneer founders had hoped. The Annual Sessions still remain its most important accomplishment, but other activities, most of which I have mentioned, are hardly less valuable. Through the establishment of the John Phillips Memorial Award and the giving of Fellowships to assist in research work, it recognizes and aids the efforts of earnest students of medicine. It owns and publishes a great medical journal. Furthermore, it is supervising the classification and certification of Internists. And it now owns a permanent home. These results, while gratifying, are not enough. We must not allow ourselves to become satisfied. Dr. Aldred Scott Warthin pointed out in an Editorial a short time before his death, that the College must develop its cultural side and take advantage of its opportunities to influence and guide medical thought in the country. I feel that now, given the right kind of leadership, with our strong organization, the College may look forward to the future with eagerness and confidence, and that it will do its part toward the forming of medical ideals throughout America.

THE AMERICAN BOARD OF INTERNAL MEDICINE*

By WALTER L. BIERRING, M.D., F.A.C.P., Chairman, *Des Moines, Iowa*

THE growth of specialism in America is in line with progress, and significant of the remarkable advancement of knowledge in every field of medicine since the opening of the century.

That modern diagnostic technic is based on special training is obvious, and its influence towards specialized medical and surgical practice is likewise apparent.

In the evolution of American medical schools during the past three decades, uniformity of curriculum and hours of study constituted all too frequently the principal standard of measurement, and in consequence, courses in certain specialties occupied a large part of the undergraduate curriculum.

This was reflected in the increasing number of medical graduates taking up one or the other of the specialties, directly upon admission to practice. The studies of Weiskotten indicated that an average of 10 per cent of recent graduates entered the field of specialized practice in 1910, and this rose to the unusual figure of 35 per cent in 1930. This state of affairs became a matter of considerable concern to medical educators, and the profession generally recognized the inherent dangers of this large influx of incompletely prepared specialists in the different fields.

With the advent of special certification, the training of specialists is definitely within the field of postgraduate medical education.

In certain of the European countries legal provisions control the licensure of specialists, but such measures did not seem practicable for this country. In the many discussions on the subject, the consensus was that the responsibility lay on the organized medical profession as represented by the American Medical Association, and that any form of legislative control was undesirable.

It is to the credit of special societies in two specialties, ophthalmology and otolaryngology, that they have taken the initiative and led the way towards the formation of qualifying and certifying boards in the different medical specialties.

The American Board of Ophthalmology was the pioneer in this field, being organized in 1916, and has been certifying specialists in ophthalmology ever since. The American Board of Otolaryngology was formed in 1923, the American Board of Obstetrics and Gynecology in 1927, and the American Board of Dermatology and Syphilology in 1929.

As other specialties began to take steps towards forming similar qualifying boards, the need was recognized for some central agency or supervising

* Presented at the St. Louis meeting of the American College of Physicians, April 22, 1937.

body such as the Council on Medical Education and Hospitals of the American Medical Association for the purpose of coördinating graduate education and the certification of specialists in the United States and Canada. A further purpose was to formulate standards of administration in general, based upon those of the four specialty boards previously organized, and to recognize new boards meeting those standards.

In order to avoid duplication of effort as well as to coördinate the work of the several boards, and other interested groups, it was deemed advisable to create an Advisory Board for Medical Specialties, which should be representative of each organization concerned. This Advisory Board began to function in February 1934. Since that time the American Board of Pediatrics, the American Board of Neurology and Psychiatry, the American Board of Radiology, the American Board of Orthopedic Surgery, the American Board of Urology, the American Board of Internal Medicine, the American Board of Pathology, and the American Board of Surgery have been formed, thus completing the organization of certifying boards in the twelve recognized medical and surgical specialties.

Each of the twelve specialty boards comprise in their membership representatives from the national special societies concerned and the section of the particular specialty in the Scientific Assembly of the American Medical Association.

The formation of an American Board for the Certification of Internists originated with the action of the Board of Regents of the American College of Physicians at the session in Philadelphia, April 30, 1935, when a resolution was adopted to coöperate with the Section on the Practice of Medicine of the American Medical Association in the appointment of a representative committee of organization.

After fulfilling the necessary requirements to obtain the approval of the Advisory Board for Medical Specialties and the Council on Medical Education and Hospitals of the American Medical Association, the Articles of Incorporation of the American Board of Internal Medicine were filed on the twenty-eighth day of February 1936.

The official organization was completed and the Board began to function on July 1, 1936. The membership of the first Board was composed of the following members: Dr. Jonathan C. Meakins, Montreal, Vice-Chairman, Dr. O. H. Perry Pepper, Philadelphia, Secretary-Treasurer, Dr. David P. Barr, St. Louis, Dr. William S. Middleton, Madison, Wisconsin, and Dr. G. Gill Richards, Salt Lake City, representing the American College of Physicians, and Dr. Ernest E. Irons, Chicago, Dr. Reginald Fitz, Boston, Dr. John H. Musser, New Orleans, and Dr. Walter L. Bierring, Des Moines, Chairman, as representatives of the Section on the Practice of Medicine of the American Medical Association.

The purpose and objective of the Board is the certification of specialists in the field of internal medicine, and the establishment of qualifications for

such certification, and of the procedure necessary for the accomplishment of such objective.

In its various announcements, the Board has endeavored not to establish any fixed rules for the preliminary training of candidates for certification in this field, but rather to outline or suggest certain broad general principles for training—subject by necessity, to constant changes reflecting the dynamic nature of the specialty.

It is generally recognized that a sound knowledge of physiology, biochemistry, pathology and the other basic sciences, insofar as they apply to disease, is essential for continued progress of the individual who practices internal medicine.

A portion of the written examination required for certification is, therefore, designed to test the candidates' knowledge of these " pre-clinical " subjects and especially in their application to disease rather than their purely laboratory aspects.

The mere factual knowledge of medicine and its basic sciences is not sufficient. The candidate must have had training in their use in furthering his understanding in clinical medicine. This implies practical experience under the guidance of older men who bring to their clinical problems ripe knowledge and critical judgment. Preparation to meet this requirement adequately may be even more difficult to obtain than the so-called scientific training. It may, however, be acquired in the following ways:

A. By work in a well-organized hospital out-door clinic conducted by competent physicians.

B. By a prolonged period of resident hospital appointments, likewise directed by skilled physicians.

C. By a period of training in intimate association with a well-trained and critical physician who takes the trouble to teach and guide his assistant rather than to expect him only to carry out the minor drudgery of a busy practice.

The Board does not consider it to the best interests of internal medicine in this country that rigid rules as to where or how the training outlined above is to be obtained. Medical teaching and knowledge are international. The opportunities of all prospective candidates are not the same. Some may have the opportunity of widening their knowledge by a period of study abroad. Others, at the other extreme, may be restricted to a comparatively narrow geographic area and their more detailed training must be obtained in short periods scattered over a longer period of time. Although it is required that at least five years must elapse between the termination of the first intern year and the date when the candidate is eligible to take the examination, a longer period is advisable. The Board wishes to emphasize that time and training are but a means to the end of acquiring a breadth and depth of knowledge of internal medicine which the candidate must demonstrate to the Board in order to justify it in certifying that he is competent to

practice internal medicine as a specialty. The responsibility of acquiring the knowledge as best he may rests with the candidate, while the responsibility of maintaining the standard of knowledge required for certification devolves on the Board.

The examination required of candidates for certification as specialists in internal medicine will consist of Part I (written), and Part II (practical or clinical).

Part I. The written examination is to be held simultaneously in different sections of the United States and Canada and will include:

A. Questions in applied physiology, anatomy, physiological chemistry, pathology, bacteriology, and pharmacology as related to internal medicine as well as the cultural aspects of medicine.

B. Questions in general internal medicine.

Part II. Candidates successful in the written tests will be eligible for the practical or clinical examination, which will be conducted by the members of the Board near the time and place of the annual meeting of the American College of Physicians and of the American Medical Association.

Two written examinations have been held, with fifty (50) candidates appearing for the examination on December 14, 1936 and thirty-six (36) on March 22, 1937.

The first practical examination will be conducted by members of the Board at the City Hospital, St. Louis, on April 23, 1937, at which thirty-five (35) candidates are expected to appear. A second practical examination will be conducted in Philadelphia on June 5, 1937. The next written test will be held in different centers in October 1937 and a practical examination will be held in Chicago in February 1937.

Certification without Examination

The organization, during the past forty years, of seven special societies concerned mainly with the advancement of internal medicine is significant of the leadership that has been attained in this specialized form of medical practice.

The desire to maintain these high standards of internal medicine has been a potent influence in developing the present plan of certification procedure.

In inaugurating this movement it seemed fitting to consider the special recognition of leading internists in the United States and Canada, who as teachers or through experience in specialized practice had distinctly contributed to the advancement of internal medicine.

It was therefore decided to consider applications for certification without examination from the following three groups:

1. Professors and associate professors of medicine in approved medical schools in United States and Canada.
2. Members or Fellows in good standing in the following special societies, who had limited their practice to the specialty of internal medicine for ten years or longer:
   - *A.* Association of American Physicians.
   - *B.* American College of Physicians.
   - *C.* Royal College of Physicians of Canada.
   - *D.* American Clinical and Climatological Association.
   - *E.* American Gastro-Enterological Association.
   - *F.* American Society for Clinical Investigation.
   - *G.* Central Society for Clinical Research.
3. Licensed physicians who had limited their practice to the specialty of internal medicine for fifteen (15) years or longer and were recommended for certification by the Executive Committee of the Section on the Practice of Medicine of the American Medical Association.

During the year more than one thousand (1000) of such applications have been received and the proper evaluation of the eligibility of each applicant has proved a more difficult problem than at first anticipated. As several months will probably transpire before final announcement can be made, the Board trusts that it may enlist the charity and patience of all those who are concerned.

The certification of the more limited specialties of internal medicine such as cardiology, gastro-enterology, allergy, tuberculosis, etc., has been given very careful consideration by the Board since its organization.

In an earlier announcement the Board published the intention to inaugurate, immediately after July 1, 1937, qualification and procedure similar to that in general internal medicine, for additional certification in the above named restricted and specialized branches.

In view of the various problems that have developed during the period of organization and institution of the general plan of certifying procedure, the Board considers that it would be more practical to defer this additional certification for the present or until the plan of certification of specialists in the general field of internal medicine is more completely established.

The general approval that has been accorded the American Board of Internal Medicine in its efforts to institute the aims and purposes for which it was organized has been most gratifying. The Board takes this opportunity to express its obligation to the Officers, Regents, Governors and Fellows of the American College of Physicians, as well as to the members of the Executive Committee of the Section on the Practice of Medicine of the American Medical Association and the officers of the several special societies of internal medicine for valuable advice and counsel extended at all times.

The Board trusts that it can continue to count on this coöperation, particularly in directing the younger physicians in courses of special training with certification in internal medicine as the objective.

It will be evident that the standard of qualifications for election to Fellowship in the American College of Physicians and in other special societies of internal medicine will be distinctly influenced by such certification.

The Board is, likewise, firmly convinced that the simple procedure of certification is of minor import as compared with the effect this movement will have in elevating the standards of medical specialists, in advancing the development of postgraduate medical education, particularly the thorough training in internal medicine, and ultimately in benefiting the patient who is at all times entitled to the highest type of medical service.

RHEUMATIC HEART DISEASE IN PHILADELPHIA SCHOOL CHILDREN *

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ABOUT 1 per cent of the 350,000 children in the public and parochial schools of Philadelphia † have some form of heart disease. The main causes of heart affection, as is well known, are congenital developmental defects, rheumatic fever and other infections, syphilis and degenerative changes. Of these causes, congenital defects and rheumatic infection, chiefly, pertain to children of school age, and rheumatic heart disease by itself constitutes by far the most frequent variety. The common age at the onset of rheumatic infection coincides with the years of the child's school attendance, namely, from five to eighteen. In fact, the child is most susceptible to rheumatic infection during the first four years of school attendance. The opportunity to study the earliest phenomena of the greatest cause of heart disease in children thus presents itself to the medical supervisor of the pupils' health.

PROSPECTUS OF THE REPORT

Briefly outlined, this report contains the following:

1. Inferences that can be drawn from the histories of juvenile rheumatic infection.
2. Prevalence of various infections in the children studied.
3. The incidence of abnormal hearts.
4. The incidence of recognizable congenital and rheumatic heart disease.
5. Classification and description of restrictions of physical activities in public schools.
6. Correlation of the functional capacity of the cardiac patient with the restricted physical activities.
7. Diagnostic aids in determining when the rheumatic infection is inactive.
8. A word as to how safely a child with heart disease can be guided through his school years.

PROCEDURE

Eleven public school physicians reviewed the medical record cards ‡ of 33,293 pupils enrolled in one school district, known as District No. 9. These medical records showed the respective school physician's findings at

* Received for publication August 12, 1936.

† Philadelphia, Pennsylvania, is a city of over two million inhabitants, and has a temperate climate. North Philadelphia, the section in which the survey has been conducted is inhabited largely by families whose social condition is a little better than the average, although about one-fifth of them are poor.

‡ A blank form will be furnished with the reprint, on request.

the annual physical examination of the pupil. Thus, unlike a previous survey [1] based on my own selection, these children have been nominated for study by the 11 medical inspectors in the schools. Of the many items found on a pupil's medical record, the following were selected: name, school, date of birth, sex, race, and grade. In addition, for each pupil a note was made of the date of the physical examination that indicated the abnormal cardiac condition, the diagnosis made or signs discovered on examination of the heart, the severity of the condition, whether the pupil had been indulging in gymnasium work, any other defect that had been discovered, and the identification number of the school physician. A notation was made of every child who had any abnormality marked under the caption of "heart," at any previous examination. Any record of "nervousness" and "chorea" was also noted. Another source of suspected heart cases was found in prolonged absences, recorded with the Compulsory Attendance Department. The Compulsory Department supervises prolonged absences, and enforces attendance. Children who are unable to attend school furnish the school which they should attend with an excuse from their private physician or report from hospital. The Compulsory Department, in the district surveyed, had on file reports on 261 children who had been absent for months or years. Twenty-four of these reports (9 per cent) showed the absences to be due to some circulatory disturbance, and these cases were included in the study. Additional names of suspected heart cases were obtained from the 28 school principals, their secretaries, and the 11 school nurses employed in this district. While there are 10 school districts in the city, the survey covered about one-eighth of the entire public school population, and about one-ninth of all the Philadelphia children of school age.

A preliminary physical examination was the next step. Of the 863 pupils examined the first time, 472 showed no evidence of heart lesion or suspicion of it, and were thus eliminated; and 391 were slated for study. A juvenile rheumatic disease blank was then provided for each case, and the history was obtained from the parent, by a school nurse or physician. For the girls, a special permission was secured to remove "sufficient clothing from the chest and shoulders" to enable the doctor to examine the chest carefully.

The physical examination of the children included mainly the parts of the body bearing on the circulatory system. An attempt was made, however, to investigate any additional points of interest, disclosed in the anamnesis or by signs revealed on examination. In all cases reëxaminations were made within the next year, and in many instances a third examination was made this year, 1936.

Inferences from the Histories

Each summarized history was placed in one of three different classes, depending on the amount and nature of evidence of rheumatic infection,

namely: "Actual," when acute rheumatic fever, chorea, or other unmistakable history of rheumatic infection was present; "Suspicious," when there was no convincing proof of actual infection; and "Negative," when there was no past or present evidence of rheumatic affection. A tabulation of all items in these histories showed tens of thousands of entries, a discussion of which would be too lengthy. Nor is it necessary. A brief comment on some of the more interesting points will suffice.

The particular school population of 33,293 pupils surveyed contained 157 children of the negro race, but of the 391 cases studied, only one was colored. Of these 391 studied cases, 214 were boys and 177 girls. Three hundred and fifty of the 391 studied showed abnormalities, either in the history or on physical examination, or in both. Of these 350 (1.1 per cent of entire school population reviewed), 191 (0.6 per cent) showed signs of organic heart disease, later to be described; 113 (0.33 per cent) pupils were recorded as showing "Abnormal signs or symptoms referable to the heart but the diagnosis of heart disease uncertain" (Class E); and 46 (0.013 per cent) were classed as children "Without circulatory disease whom it is advisable to follow because of the presence or history of an etiological factor which might cause heart disease" (Class F). These two classes and their quoted definitions are in compliance with the Standard Classification and Diagnosis of Heart Disease as accepted by the American Heart Association.

Classes E and F should form interesting groups for observation, prolonged if possible, even after the pupils leave the public school. Will they establish their freedom from heart affection, retain their functional heart conditions, or develop organic heart disease? If the last should happen, one would like to know under what circumstances it has occurred, and if it was possible to prevent it.

It is interesting to note that in the final classification eight children with organic heart disease had entirely negative histories as far as any infection allied to juvenile rheumatic disease, or known congenital maldevelopment is concerned. On the other hand, five pupils with actual histories of past rheumatic infection, 45 with suspicious histories, and 63 with negative histories were among those children in Class E. Five children with actual histories, 19 with suspicious histories, and 22 with negative histories belonged to Class F. Thus, it is quite possible that, had histories been obtained on all 863 nominated pupils, and had the 472 children not been entirely eliminated at the first examination that additional children with heart disease would have been discovered. Also, more children might have been found belonging to Class E or F.

In the subsequent discussions of points in the anamnesis, the numbers and percentages refer to the 350 pupils with abnormal hearts. Children belonging to Classes E and F have been included in this discussion.

Discussion of Some Manifestations

Tonsillitis. Of the 140 children (40 per cent) that had tonsillitis, 61 had an occasional attack, 53 had few attacks, 21 had many attacks, and 5 had very many attacks. The total number of children that had tonsillitis at the ages of three, five, and six, was one and one-half times the total number of cases of all the children of all other ages between two and fourteen. In fact, almost one-half of all the children that had tonsillitis had their first attacks at the ages of five and six. Within a year of the first attack of tonsillitis, 43 children had their tonsils removed, and before two years passed, 37 more had the operation. Altogether 101 children who had had tonsillitis subsequently had tonsillectomies, but there were 11 additional children who gave a history of tonsillitis after tonsillectomy. A total of 110 children had no history of tonsillitis yet had tonsillectomies, and only 28 that had had tonsillitis had no tonsillectomies. Of the 65 children that had acute rheumatic fever, 36 had tonsillectomies before the first attack of rheumatic fever, 15 after it, and 14 children had no tonsillectomies. Of the 39 pupils that had chorea, 15 had their first attack before tonsillectomy, 17 had it after the operation, while seven had retained their tonsils. One can infer from these data, among other things, that the popular operation of tonsillectomy is often inadequate to prevent entirely or to ameliorate without fail all cases of chorea, acute rheumatic fever or rheumatic heart disease. Even tonsillitis itself had occurred after some tonsillectomies.

Acute rheumatic fever was present in 18.6 per cent of the histories. More children had their first acute attack of rheumatic fever, *recurrent fever,* and *involuntary twitchings* at the age of seven than at any other age. The number of attacks of rheumatic fever varied from one to five, the last mentioned being in a child whose first attack occurred at seven.

Chorea occurred in 11 per cent. The first attack of chorea occurred in more children at eight years of age than at any other age. At the ages of seven and five the next larger number of children had their first attack.

A greater number of children had their first or only attack of *recurrent unexplained abdominal pains, joint pains, swelling of joints, pain in the region of the heart, "heart disease,"* and *scarlet fever* at five years than at any other age.

Enuresis occurred for the first time most frequently in children of nine years, *severe muscle* or *"growing pains,"* at 10 years of age, and *"heart failure"* at eleven. An equal number of children had their first attack of epistaxis at eight and 12 years of age. The onset of *sinus disease* was noted most frequently in the twelfth year, although it began almost as frequently in the third and sixth years. Dental infection was present in 52 per cent of the children.

Familial Predisposition. The insidiousness of the onset of many cases of rheumatic heart disease and the chronicity of the asymptomatic stage of the heart affection make one suspect the possibility of familial incidence of

the disease, as in tuberculosis. This was borne out in this survey. Among the 350 cardiacs 79 (22.6 per cent) had a history either of some near relative having heart affection or of a sibling with rheumatic heart disease. These relatives were as follows: 29 grandparents; 20 mothers; three fathers; both parents (one instance); other relatives (eight instances); nine brothers and nine sisters. Four pairs of siblings were under observation. Unfortunately, it was not ascertained whether among the adults there were some suffering from other than rheumatic heart disease—which was very likely. In view of this incidence of rheumatic heart disease in the family, examination of every available member of the family is advisable, once a member is found to have rheumatic heart disease.

A brief summary of the actual, suspicious and negative histories of the 391 cardiac suspects is shown in the following table:

TABLE I

Prevalence of Conditions in 391 Histories

Conditions in order of prevalence	In children with			Total
	Actual rheumatic history	Suspicious rheumatic history	Negative history	
Measles	80	116	121	317
Pertussis	59	70	76	205
Tonsillitis	44	62	34	140
"Heart disease"	57	54	24	135
Severe muscle or "growing pains"	38	58	16	112
Recurrent common colds	25	37	21	83
Heart pains	33	46	4	83
Chicken pox	27	20	20	67
Acute rheumatic fever	58	7	0	65
Scarlet fever	21	29	10	60
Recurrent unexplained abdominal pains	21	35	2	58
Pneumonia	13	22	20	55
Involuntary twitchings	35	16	4	55
Joint pains	29	24	1	54
Epistaxis	20	16	12	48
Recurrent fever	24	14	3	41
Mumps	18	13	10	41
Chorea	38	1	0	39
Enuresis	10	19	9	38
Diphtheria	8	17	10	35
Influenza	12	15	3	30
Swelling of joints	17	4	1	22
Sinus disease	4	11	6	21
"Heart failure"	8	8	4	20
Nodules under the skin	2	1	0	3

PHYSICAL EXAMINATIONS

Mindful of the inference drawn from the history, each girl as well as boy was examined with bared front of the chest. There were just as many pupils with rheumatic cardiac affection whose general appearance was fair or good as there were of poor appearance. Twenty-one showed choreiform

movements. Pallor and fever were found in a smaller percentage of children examined in school than in those examined at home. Tonsils were present in almost 50 per cent of the children. Two-thirds of the children had enlarged glands in the neck. A pulse rate of over 100 per minute was not found indicative of rheumatic affection, as many children without signs of heart disease also had that rate. The temperatures of a number of children were above 99° F. (by mouth). For the sake of brevity, diagnoses will be stated without enumerating the accepted diagnostic signs or criteria. I wish to introduce and discuss, however, a new anatomical landmark used for the anterior chest wall.

A New Landmark on the Chest Wall

In recording cardiac enlargement I have been in the habit of designating the point midway between the midclavicular and anterior axillary lines as the "preaxillary" line, adding the interspace at which the apex beat was felt. The preaxillary line is an imaginary line on the front of either side of the chest, drawn vertically downward, midway between the midclavicular and anterior axillary lines, and parallel to them. It divides vertically the surface area of the chest wall between the midclavicular and anterior axillary lines exactly in half. Unlike the parasternal line which is similarly drawn from the medial half of the clavicle, the preaxillary line does not take origin from the outer half of the clavicle. Although I do not remember seeing any reference to such an anatomical landmark, I find it more convenient and descriptive than any measured distance from the midclavicular line. The preaxillary line seems to me to have a more constant relation to the person's chest as it is applicable to a patient of any age, size, or stature. Furthermore, one can express the relation of the apex beat to the preaxillary line by stating whether the apex beat is near or beyond this line. The apex beat may be located midway between the midclavicular and preaxillary lines or between the preaxillary and anterior axillary lines. Such a descriptive location of the apex beat seems to make possible a more constant anatomical site of the finding. A given measured distance in centimeters or inches would not be so self-explanatory, for one must know the approximate size of the chest. What is true of the use of the preaxillary line for the apex beat is also true for designating the margin of cardiac dullness, and flatness of pericardial effusion. Less frequently, the preaxillary line on either side may be used to designate the outline of pathologic pulmonary or pleuritic structures, as in extracardiac foreign bodies, consolidations, effusions or neoplasm in the chest.

Diagnoses of Heart Disease

A diagnosis of organic heart disease, congenital or acquired, was made in 191 pupils. Briefly, the diagnoses were as follows:

Etiological Diagnosis:	No. of Cases
Congenital developmental defect	28
Congenital developmental defect combined with acquired heart disease, rheumatic	2
Rheumatic heart disease, active and inactive	129
Measles	1
Scarlet fever	8
Hypertension	4
Nephritis	1
Unknown (probably rheumatic)	18
Total	191

Anatomical Diagnosis:

Congenital cyanotic lesion (tetralogy of Fallot)		4
Congenital acyanotic lesion		24
Hypertrophy of heart, including 3 cases with chronic adhesive pericarditis		44
Cardiac valvular disease, including 2 having also congenital acyanotic lesions		118
Aortic insufficiency, including 1 with chronic adhesive pericarditis	8	
Double aortic lesion	1	
Aortic insufficiency and double mitral	1	
Double aortic and double mitral	1	
Mitral insufficiency	42	
Mitral stenosis	21	
Double mitral	44	
Aortitis		1
Total		191

Physiological Diagnosis. Disregarding sinus arrhythmia, which is found both in normal children and in children with heart disease, four pupils showed pathologic conduction systems, as follows: two had heart blocks, one had left and right premature ventricular beats with some intraventricular conduction delay, and one had premature contractions of which the point of origin remained unknown, as there was no opportunity for electrocardiographic study.

The *Functional Classification* varied in a number of children during the period of observation, but on the average, the cardiac capacity for exertion was as follows:

	No. of Cases	Per Cent
Class 1	131	68.6
Class 2a	41	21.5
Class 2b	15	7.9
Class 3	4	2.1

TABLE II

Heart Conditions in School Children Surveyed

Total number of pupils' medical records reviewed 33,293

	Number of children	Per cent
Pupils with suspected cardiac abnormality nominated by school physicians for study	863	2.6
Pupils for whom medical histories were obtained	391	1.14
Abnormal symptoms or signs relative to the heart were found in	350	1.05
Organic heart disease	191	0.6
Congenital heart disease (including two having also acquired lesions)	30	0.09
Acquired heart disease	161	0.5
Class E	113	0.33
Class F	46	0.13
No heart abnormality	41	

When the school population was divided into the younger and older children, or elementary and high school pupils, the respective enrollments and incidence of heart abnormalities found were as follows:

TABLE III

Heart Abnormalities in Younger and Older Children

	Elementary school (ages 6–14 years)		High school (ages 15–18 years)		Total	
No. of pupils on roll	24,193		9,154		33,293	
	No.	Per cent	No.	Per cent	No.	Per cent
Organic heart disease	111	0.5	80	0.9	191	0.6
Class E	74	0.3	39	0.4	113	0.33
Class F	30	0.12	16	0.2	46	0.13
Total abnormal hearts	215	0.9	135	1.5	350	1.1

RESTRICTION OF PHYSICAL ACTIVITIES

To insure the teacher's coöperation in restriction of the pupil's physical activities in school, the physician treating the child certifies on a blank form as to the duration and the cause of the excuse from exercises. The school physician may act for the family doctor. In either case, the certificate may be honored for 1, 2, or 3 months, and has to be renewed thereafter, unless it is endorsed by the medical supervisor. The supervisor has the authority to approve the certificate for a longer period of time, or even for the duration of the pupil's entire school life. In addition to the cause and duration of the restriction of physical activities, the exercises allowed are indicated and checked on the certificate as follows:

1. Competitive sports, requiring considerable exertion.
2. Vigorous exercises on gymnasium apparatus. Running and jumping.
3. Calisthenics and general exercises, simple games and play. These activities require little running or muscular effort.
4. Very mild exercises (movements of arms, legs, neck and trunk)—duration 10 minutes.
5. Very mild exercises (movements of arms, legs, neck and trunk)—duration five minutes.

These listed physical activities are not descriptive of the degree of exertion required. I have therefore secured from the director of physical and health education, Mr. Grover W. Mueller, an interpretation of the classifications which appear on the certificate. The numbered physical activities are briefly described by Mr. Mueller, as follows:

INTERPRETATION OF CLASSIFICATIONS OF RESTRICTION OF PHYSICAL ACTIVITIES

1. Football; basketball; soccer; track and field events; lacrosse; field hockey; ice hockey; wrestling; boxing; competitive swimming, etc. These activities are characterized by vigorous activity, many moments of minimum effort, and many instances of sustained effort. The competitive element stimulates continuation of effort and participation which in the absence of such stimulus would be interrupted by intervals

of rest or relative inactivity. Speed, endurance, effort, and skill are the main physical qualities involved. Stimulation of the emotions and of the circulatory and respiratory systems is pronounced.

2. Vigorous exercises on the parallel and horizontal bars, rings, horse, buck and mats; hopping and jumping; vigorous dancing, such as folk dancing; non-competitive running, except that the running often is a part of competitive games of low organization, thus often resulting in vigorous running. The activities on the apparatus are characterized by the physical qualities of strength and skill; the running, hopping, and jumping are characterized by stimulation of the circulatory and respiratory systems. Great momentary effort frequently occurs, but effort is not sustained for more than a few moments, and stimulation is not nearly so great as in Group 1. Emotional stimulation is slight.

3. General free exercises (calisthenics); mild forms of dancing; mild exercises on apparatus which are done in hanging and sitting positions; simple games and play. These activities involve mild contraction and extension of most of the muscle groups. The activity is alternated with regular short intervals of rest, effort is neither great nor sustained; there is only slight physiological stimulation; strength is involved only momentarily and in slight degree; skill is involved, consisting mainly of hand, arm, and eye coördination. Running is either in one spot or over short distances at moderate speed. The competitive element is lacking entirely, and no emotional stimulus is involved.

4. General free exercises (calisthenics) and simple play forms. These free exercises involve very mild contraction and extension of most of the muscle groups. They differ from those in Group 3 in that the exercises are more localized, they are not repeated so often, the intervals of rest are more frequent and of longer duration, and many of the exercises are done in the sitting and lying positions. Pupils may stop at any time they feel tired. Some exercises are done against mild resistance set up by a second person. The play forms involve little effort and consist almost entirely of hand, arm, and eye coördination, such as throwing rubber quoits, and throwing a ball over a short distance at a goal. In none of these exercises is strength involved except in the mildest possible degree. Running, hopping and jumping as well as any other activity which stimulates the circulatory and respiratory systems in any but the mildest degree are omitted entirely.

5. The activities in this group are identical with those in Group 4. The difference in the two groups is entirely in the total amount of physical work done. In Group 5 half as much work is done in one-half as much time (5 minutes) as in Group 4 (10 minutes).

Depending on the degree of the pupil's handicap there are four more listed "physical activities" each requiring less and less energy in successive degrees:

6. Walking only—10 minutes.

7. No exercise, but ordinary activity throughout the school day.

8. No exercise. Full day attendance. Rest during recess period. Pupil is allowed to move from room to room and to use stairs without regard to movement of classmates. Use of school elevator if there is one.

9. No exercise. Same privileges as number 8. Pupil is allowed to stay home in the afternoon to rest, whenever necessary.

The above classification of restrictions of physical activities has a definite relation to a pupil's physical capacity for exertion. It may be well therefore, to recollect at this time the standard classification of Functional Capacity

approved by the American Heart Association, and later discuss the application in school of the classification of restricted physical activities to the given functional capacity of the pupil with heart disease. The two together will permit a better correlation between the pupil's routine in the school and the cardiac capacity for exertion.

Functional Classification of Patients with Organic Heart Disease

Class 1. Patients with organic heart disease, able to carry on ordinary physical activity without discomfort.

Class 2. Patients with organic heart disease, unable to carry on ordinary physical activity without discomfort.

a. Activity slightly limited.

b. Activity greatly limited.

Class 3. Patients with organic heart disease and with symptoms or signs of heart failure when at rest, unable to carry on any physical activity without discomfort.

Correlation of Functional Capacity with Restrictions of Physical Activities

I am frequently faced with the problem of correlating the functional capacity of the child with heart disease with the restriction of physical activities in the school. At times I am asked to endorse the family physician's request for the same. Children have to be guarded against participating in physical exercises to a prohibitive degree and against failing to indulge in permissible activities. The former may aggravate the cardiac condition or, through fatigue, lead to serious accidents, while the latter deprives the pupil of a necessary amount of physical culture and scholastic development. As a rule, though, it is safe to assume that the average child with heart disease will do all he can. Only in rare instances, as in the child who is not proficient in the activity, will he attempt to dodge the gymnastic requirement of the curriculum. Although a child with a Functional Capacity of Class 1, for instance, can usually be as active as any child that has no heart disease, it is not advisable to permit him to indulge in competitive sports which may over-stimulate activity beyond his endurance. Rather, it seems to me, the pupil should indulge in physical activities to a moderate degree that will satisfy his desire for athletics, and yet avoid risking a possible temporary heart failure or permanent aggravation of the heart condition. The avoidance of overexertion is very important, and the ability of a patient with organic heart disease "to carry on ordinary physical activity without discomfort" does not seem to me to be so universally applicable to school children as to adults. High school pupils, especially, routinely indulge in vigorous physical training and competitive sports which may call for *extra*-ordinary physical activities that are not safe for one with heart disease, even if the functional classification is class 1.

Furthermore, the older children, in the high schools, can be taught the danger signals, and warned to cease activity upon becoming aware of palpi-

tation or dyspnea. The younger children, however, in the elementary schools, may frequently fail to remember these sensations of heart beating and shortness of breath. Taxing the heart that has a chronic structural defect, such as valvular lesion, with a great amount of non-competitive activities may be often harmless. When heart disease is in the active stage, however, the problem is a more difficult one, and much greater precaution has to be exercised against further damaging the myocardium or causing a reactivation of a quiescent lesion. In other words, a strain on the mechanical defect of the circulation is of little danger. Inflammation, or activity of infection, however, requires not only restricted activities, but rest and prolonged convalescence for arrest or recovery of the process. Some systemic conditions as underweight, overweight, or the presence of other relevant physical defects in cardiacs may also require a suitable modification of the general principles of restriction of physical activities. When a complete cardiac diagnosis (etiological, anatomical, physiological and functional) is considered together with the full meaning of the numbered physical activities, the correlation of the functional capacity of the cardiac with the restriction of physical activities in the school becomes facilitated. Still, it is difficult to be dogmatic, as cardiacs with different anatomical diagnoses, although having the same functional classification, may require different restrictions of physical activities. I realize also, that my correlations may appear to some physical health educators to be too conservative, and to some physicians to be too radical. Experience has shown, however, that to err on the safer side is a mistake on "the side of the angels." I have therefore been recommending the following correlations:

TABLE IV

Correlation of Functional Capacity with Restriction of Physical Activities

Functional capacity	Physical activity Number allowed (highest)
(No school child with organic heart disease)	No. 1
Class 1 (mild cases of congenital acyanotic or acquired lesions)	No. 2
Class 1 (depending on the anatomical and physiological diagnoses)	No. 3, 4 or 5
Class 2a	No. 6 or 7
Class 2b	No. 8 or 9
Class 3	No. 9

WHEN IS RHEUMATIC INFECTION INACTIVE?

The question of whether rheumatic heart disease is in the inactive stage is particularly important to decide before the child is allowed to attend school, or return to it after any acute illness. As previously mentioned, the problem is also vital for the determination as to how much the child should be allowed to do in the school. It may be well, therefore, to review the his-

tory, physical signs and other findings that assist in ruling out activity of rheumatic infection.

During the inactive stage of rheumatic infection.

1. The child is free from any symptoms relevant to the infection.
2. He presents a good general appearance and absence of pallor or cyanosis.
3. He has good body weight.
4. He has a rectal temperature of 100° F. or less.
5. His pulse rate is not over 100 a minute, and after exercise the rate returns to pre-exercise rate within three or four minutes.
6. He is free from fatigue when not exercising.
7. His systolic blood pressure and pulse pressure are within normal limits.
8. There is cessation of increasing cardiac enlargement.
9. There is freedom from evanescent adventitious pericardial, myocardial or endocardial sounds, pathologic conduction, or signs of heart failure.
10. There is freedom from a focus of active infection, as in the upper respiratory passages.
11. There is freedom from rheumatic nodules, skin eruptions, or hemorrhages.

Further investigations confirming the inactivity of the infection are:

12. A normal hemoglobin, and red and white cell counts.
13. A sedimentation rate within normal limits.
14. A normal respiratory vital capacity.
15. An electrocardiogram that is free from deviations suggestive of rheumatic heart disease. (Although not pathognomonic, prolongation of the P–R interval, alterations of the rhythm normal to children, and certain S–T or R–T and T-wave changes are characteristic deviations from electrocardiograms that might otherwise be considered within normal limits.)
16. An unchanging cardiac contour on roentgenologic and esophagraphic tests.

Does Heart Disease Become Worse During School Years?

Whether school life aggravates a child's heart condition depends much on several factors entering into the condition of the cardiac and his hygiene of life. It depends on an early complete cardiac diagnosis, a suitable restriction of physical activities, avoidance of school attendance during the active stage of the infection and, as previously mentioned, adequate convalescence after any other disease before school attendance is resumed. In my experience, heart disease frequently develops during—not necessarily because of—school activities, and in many cardiacs the condition becomes aggravated during the average twelve years of education. Space does not permit the citation of numerous examples. On the other hand, I have seen

many pupils who have gone through their greater part of school life with hardly any aggravation of the cardiopathy. It is true that a person with rheumatic heart defects can usually live comfortably the larger part of the span of expected life, but there are exceptions. Generally speaking, the prognosis of the child with heart disease depends on the early discovery of the condition, the degree of cardiac enlargement, the state of myocardium and the particular valves involved, the rhythm, the exercise tolerance, the education and preparation for a vocation with minimum additional damage to the heart, and the selection of a suitable vocation and harmless avocations.

Conclusions

1. The medical records of 33,293 children enrolled in Philadelphia public schools have been reviewed for abnormal heart findings. Of 863 pupils listed for observation of their hearts by 11 school physicians, 391 were considered worthy of studying. The study has been made with the aid of an adequate history of juvenile rheumatic infection, and physical examinations for the detection of circulatory diseases. Examination was made twice at an interval of about one year, and in many cases, a third examination was made in 1936. The thermometer, stethoscope, and blood pressure apparatus were used, but, with several exceptions, no other instrument of precision was employed.

2. For recording moderate cardiac hypertrophy, a new landmark on the anterior chest wall is being suggested. Its name is "preaxillary" line. The preaxillary line is an imaginary line on the front of either side of the chest, drawn vertically downward, midway between the midclavicular and anterior axillary lines, and parallel to them. It divides vertically the surface area of the chest wall between the midclavicular and anterior axillary lines exactly in half. Unlike the parasternal line which is similarly drawn from the medial half of the clavicle, the preaxillary line does not take origin from the outer half of the clavicle. The advantages of the use of the preaxillary line in chest examinations are described.

3. It is agreed that the parents, the family physician, the pediatrician, the cardiologist, and the hospital clinics form the main agencies protecting the children against the spread and aggravation of juvenile rheumatic heart disease. However, it is suggested that the school physician and nurse, and the school principal should also be enrolled in a permanent campaign to assist in the detection and amelioration of rheumatic heart disease in children. The school years are a very important period in the child's physical life and development, and have greater potentialities for the good or evil of a child with heart disease than of a healthy pupil. Perhaps the combined efforts of those named above can guide many of these unfortunate children more safely through the early educational years, prepare more wisely for a suitable vocation, and at the same time choose safe avocations. It is possible that such

wholehearted coöperation may reverse the tide, and cause a decrease in the incidence of rheumatic heart disease, not only in children, but in adults.

Acknowledgments. Directly and indirectly, a number of physicians, a greater number of nurses and clerical assistants, have kindly helped to assemble the data which made this report possible. Several school principals have coöperated even to the extent of arranging for physical examinations after the schools had officially closed. I regret the names are too numerous to mention here. I shall therefore be able to express my gratefulness only to Dr. Walter S. Cornell, Director, Medical Inspection of Public Schools, for his valuable advice, Drs. Samuel Baron and M. W. Benjamin, for their frequent help, and Miss Fay Ziegler and Miss Marie A. Gallagher for their diligent work in tabulating the data. Finally, may I be pardoned if I specifically mention here my great obligations to my wife in the preparation of this report.

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GONOCOCCAL ENDOCARDITIS TREATED WITH ARTIFICIAL FEVER (KETTERING HYPERTHERM) *

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It has been known for many years that the gonococcus is quite susceptible to heat.[1, 2] It remained for Carpenter, Boak, Mucci and Warren [3] to determine by careful thermal death time gradient studies that 99 per cent of the cultures of several strains of gonococci are killed in vitro by 4 to 5 hours exposure to a temperature of 105.8° F. With the Kettering hypertherm even higher temperatures over longer periods of time may be administered to patients with comparative safety. The excellent clinical results obtained with this form of treatment in various gonococcal infections strongly suggest that the thermal death point of the organisms in vivo approximates that found to exist in the in vitro experiments of Carpenter et al.

Within the last 15 years numerous authors have reported case studies of gonococcal endocarditis.[4, 5, 6] A uniform feature of the reports has been the expression of a gloomy attitude regarding the efficacy of any form of treatment, once the organism has become established on a heart valve. The present communication is concerned with the results obtained by treating one case of verified and one of probable gonococcal endocarditis with artificial fever (Kettering hypertherm).† The former is reported in detail as there have been no reports of necropsy findings in patients with gonococcal endocarditis who died after fever treatment.

Case I

History: L. L., a colored man of 24, was admitted to the Vanderbilt University Hospital July 15, 1936, complaining of weakness and chills. Five weeks previously he developed coryza, sore throat, non-productive cough, slight pain in the upper midportion of the chest, generalized aching, malaise and fever. A few days later a chill occurred, followed by slight swelling of the ankles, left knee and right elbow. These joints remained painless and the swelling lasted only a few days. After 10 days confinement to his home he felt much better although he did not entirely recover. On July 10 he noticed a sudden increase in weakness and malaise. He became dyspneic on exertion and developed edema of the feet and legs. The next day he had a chill lasting 30 minutes. On July 15 he had a second chill and his temperature was 105° F.

There was no history of gonorrhea or syphilis.

Physical Examination: He was a well developed and well nourished negro who appeared acutely ill. He perspired freely and the respirations were fast and deep. The sensorium was clear. The mucous membranes and conjunctivae were pale and

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† This apparatus was supplied to Vanderbilt University Hospital through the kindness of Mr. C. F. Kettering, director of the Division of Research, General Motors Corporation, and Dr. Walter M. Simpson, Miami Valley Hospital, Dayton, Ohio.

slightly icteric. The skin was hot (temperature 104.4°) and exhibited numerous small red lesions over the tibiae. These were 1 to 3 mm. in diameter and did not blanch on pressure. The nasal mucosa was injected and swollen. The tonsils were moderately large and reddened. The lungs were normal on physical examination. No cardiac enlargement was noted, but there was a long, loud, harsh systolic murmur of maximum intensity at the apex and transmitted to the left axilla and over the entire precordium. The second pulmonic sound was accentuated. The pulse was rapid (100), regular and of good volume. The blood pressure was 118 mm. of mercury systolic and 80 diastolic. The abdomen was distended and signs of a small amount of free fluid were present. The liver edge was firm and smooth and extended 4 cm. below the right costal margin. It was not tender. The spleen could be felt 5 cm. below the left costal margin. A circumscribed smooth scar was present on the prepuce. The prostate was normal in size but slightly soft. The joints were normal. There was moderate pitting edema of the feet and legs.

Laboratory Data: Urine, clear and yellow; specific gravity 1.008; acid reaction; no albumin and no sugar; the sediment contained occasional white blood cells but no red blood cells or casts. Red blood cell count 3,550,000; hemoglobin 8.5 gm.; white blood cell count 15,100; neutrophiles 61 per cent; eosinophiles 1 per cent; lymphocytes 33 per cent; monocytes 5 per cent; no malarial parasites. The Wassermann reaction and the Kahn test were positive. Non-protein nitrogen 21.4 mg. per cent; icterus index 9; total serum protein 7.07 gm. per cent (albumin 2.62; globulin 4.45). Stools were of normal appearance and showed no pus, blood or parasites. Bromsulphalein liver function test: 40 per cent retention in 30 minutes. The Takata-Ara test was positive. The galactose tolerance test showed a decrease in tolerance. The red blood cells exhibited normal resistance to hypotonic salt solutions. Roentgen-ray examination of the chest, pelvis and abdomen was essentially normal. Agglutination tests with *B. typhosus, B. paratyphosus* A, B, *B. melitensis* and *B. abortus* were all negative.

Course: He ran a septic course with constant leukocytosis (averaging 12,000), intermittent fever with daily fluctuations of 6 to 10 degrees and occasional chills. Jaundice and ascites slowly but steadily increased. Frequent examinations of "thick drop" preparations for malarial parasites were negative. He was given a therapeutic test with quinine for five days, without notable change. During the three weeks preceding death (August 14) he received weekly injections of bismuth salicylate and was given 25 drops of a saturated solution of potassium iodide three times daily. Blood cultures obtained July 16, 17, and 20 showed no growth, while those obtained July 22 and 29 and August 6 contained gonococci. On August 6, the urine showed a small amount of albumin, bile, a few erythrocytes and leukocytes and numerous granular and cellular casts. Evidence of renal damage rapidly increased. By August 8, the 24 hour urine excretion had fallen from 2,000 to 400 c.c., in spite of a fluid intake of over 2,500 c.c., and the urine contained a moderate amount of albumin, bile, and numerous red blood cells. On August 8, 3,500 c.c. of turbid reddish yellow fluid were withdrawn from the peritoneal cavity; its specific gravity was 1.004; the erythrocyte count 5,625; leukocyte count 1,875. No bacteria were demonstrated by smear, culture or guinea pig inoculation.

With full recognition of the extremely gloomy prognosis because of the presence of gonococcal endocarditis associated with severe liver and renal damage, he was placed in the Kettering hypertherm on August 10. His temperature was maintained at an average level of 105.5° F. (rectal) for six hours. To our surprise he bore this treatment fairly well. He was afebrile for the next 20 hours and his temperature never returned to as high a level as had previously existed. However, he appeared more stuporous. His 24 hour excretion of urine was 700 c.c. On August 11 a blood culture was made from which no gonococci were grown. On August 12 he became anuric. On August 13 he received his second fever treatment. On this occasion his

temperature was held between 106 and 107°, averaging 106.7°, for five hours. This treatment, as the first, was apparently well tolerated. However, the stupor increased and he remained anuric (non-protein nitrogen 133 mg. per cent; carbon dioxide combining power 29.1 volumes per cent). He died on August 14.

Clinical Impression: Acute bacterial endocarditis (mitral valve), due to gonococcus; syphilitic cirrhosis of liver; ascites; jaundice; embolic glomerular nephritis; uremia; anemia, secondary to infection.

Necropsy Report: Autopsy performed two hours post mortem. The sclerae, subcutaneous fat and, in varying degrees, the viscera were jaundiced. Peritoneal cavity: Contained about 1,000 c.c. of greenish-red fluid. Pericardial cavity: The surfaces were smooth and glistening; about 40 c.c. of clear fluid were present. Heart: Weight 270 grams; epicardium, myocardium and all valves, except the mitral, appeared normal. On one mitral leaflet was a firm non-friable vegetation 6 to 9 millimeters above the surface. On the opposite leaflet was a similar but smaller vegetation. These vegetations were so firmly adherent that it was felt certain that they contained a great deal of fibrous tissue (figure 1). There was slight ulceration of the margin of one cusp. The chordae tendineae appeared normal. Lungs: A small amount of atelectasis was present in the lower lobes. Gastrointestinal tract: Negative. Liver: Weight 1,800 grams; the surface was nodular and in several places broad fibrous bands cut deep in the parenchyma (figure 2). A flattened, tongue-like projection extended over the spleen. Much resistance was encountered in slicing the liver. Cut sections revealed extensive scarring with broad fibrous bundles interlacing and surrounding islands of raised, reddish-yellow tissue. Scattered here and there, but denser in the left lobe than elsewhere, were varying sized and shaped grayish yellow, soft areas of necrosis with surrounding red zones. The gall-bladder and bile ducts appeared normal. Spleen: Weight 940 grams; the pulp was firm, dark red, friable and densely studded with infarcts of varying ages, some of the older ones having become somewhat softened. Kidneys: The weight of the right kidney was 210 grams, and the weight of the left kidney was 200 grams. The capsules stripped easily, leaving smooth surfaces. The cut surfaces were pale and showed many small reddish splotches, thought to represent small hemorrhagic foci with some necrosis. Genito-urinary tract: The ureters, bladder, seminal vesicles, epididymes and prostate were normal. Brain: Negative.

Microscopic Examination: Heart: Nothing remarkable was found except in the mitral leaflets. At the site of the vegetations were seen dense hyalinized fibrin deposits containing scattered polymorphonuclear leukocytes. There were two small foci of polymorphonuclear leukocytes beneath the surface of the valve. Beneath this process was a more chronic inflammatory reaction with an associated healing reaction as evidenced by the invasion with many fibroblasts and the formation of many small blood vessels (figure 3). Lungs: Atelectasis and slight passive congestion were present. Liver: The normal architecture of the liver was almost entirely destroyed. The sections showed a very large amount of fibrous tissue encircling varying sized islands of liver cells. In the fibrous tissue were many bile ducts, scattered lymphocytes, plasma cells and macrophages. In some areas there were polymorphonuclear leukocytes in and around the ducts. All the liver cells in some of the lobules were normal, whereas others had normal cells in the periphery, but the entire midzonal and central part showed uniform karyolysis of both nucleus and cytoplasm. At the edge of these areas of necrosis were rows of polymorphonuclear leukocytes. No thrombi were seen in vessels. No typical gummata were present. Spleen: There was marked engorgement of all sinuses and hemorrhages were scattered throughout the organ. Many polymorphonuclear leukocytes were present in the pulp. There were many areas of necrosis partly infiltrated with blood which had the appearance of infarcts. There was a proliferation of fibroblasts in some of these areas. Pancreas: One acinus

FIG. 1. Healing gonococcal vegetations on mitral valve. Arrow 1 indicates a small ulcerated vegetation undergoing healing. Arrow 2 indicates the site of a lesion in which the healing process is more advanced.

FIG. 2. Liver. Note the typical cirrhotic changes on the surface of the organ and the huge scars with resulting deformity (hepar lobatum).

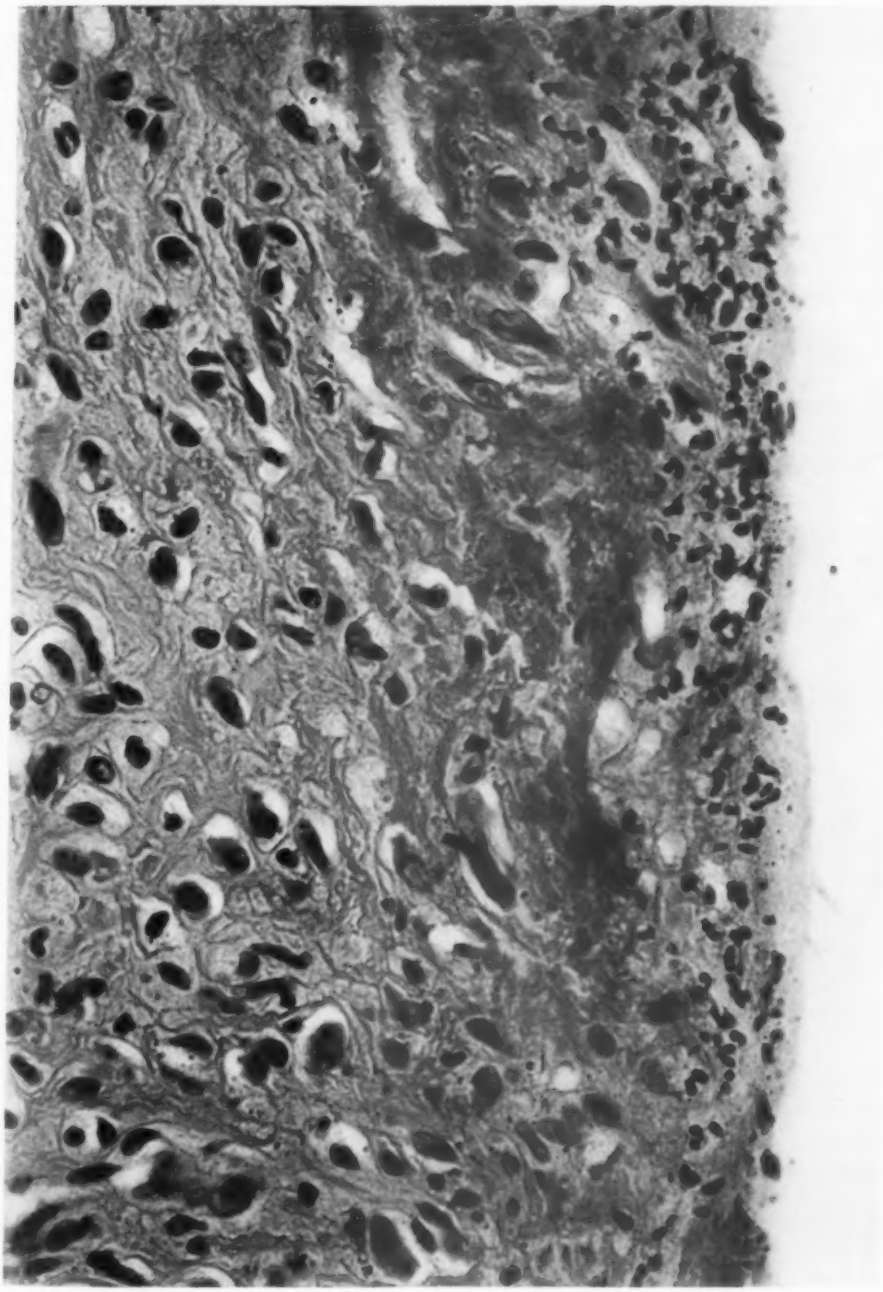

FIG. 3. H and E stain: Healing on mitral valve. (× 500.) (See figure 1.)

showed polymorphonuclear cells in its lumen whereas the remainder appeared normal, but there was edema and slight lymphocytic infiltration in the interstitial tissue. Adrenals: There was congestion of the vessels surrounded by foci of mononuclear cells but otherwise the organs were normal. Kidneys: There was swelling of the glomerular endothelium and a few of the endothelial cells were pyknotic. Many of the glomeruli showed intra-capillary hyalinization. The capillaries contained an increase in polymorphonuclear leukocytes. Some of the tubules contained polymorphonuclear leukocytes and albuminous material. The interstitial tissue was infiltrated with macrophages, plasma cells and lymphocytes. Seminal vesicles, epididymis, testis, bone marrow and brain: Essentially negative. *Bacteriology:* Smears and cultures from the vegetations yielded no organisms. Cultures of the heart's blood gave no growth. Smears from the prostate, liver and spleen contained no organisms. Stains of the mitral vegetations with hematoxylin-eosin, Gram's iodine and Giemsa stain failed to reveal organisms.

Anatomical Diagnosis: Acute endocarditis, mitral, gonococcal; syphilitic cirrhosis of the liver; infarcts in spleen, embolic; acute nephritis, embolic; pulmonary atelectasis, obstructive (with mucus); passive congestion of lungs; icterus, ascites.

This case report is of especial interest because of the following points: (1) an extremely ill person was treated in the Kettering hypertherm without treatment complications, and (2) following treatment with hyperthermia gonococcemia disappeared ante mortem, and the heart's blood and gonococcal vegetations were found sterile post mortem.

The clinical diagnosis was difficult because of the co-existing liver disease. By the time the data were correctly analyzed the patient had experienced a progressive septic illness for five weeks and exhibited evidence of severe liver disease and renal damage with uremia. His condition was such (uremia, hepatic insufficiency) that it was felt that he might not survive the first fever treatment. However, it was well tolerated. A blood culture taken the following day was sterile. The second treatment resulted in no reaction which could be related to hyperthermia in spite of the fact that the uremic state steadily progressed. At necropsy no organisms could be grown from the mitral vegetations or heart blood and none could be found on smear or with special tissue stains. There was but a small amount of fibrin and only a few polymorphonuclear leukocytes at the site of the vegetations and evidence of healing was well established.

The areas of necrosis in the liver were interpreted as resulting from emboli or from an exacerbation of syphilitic endarteritis brought about by the combination of bismuth, iodides and heat. The possibility that fever treatment may have intensified the manifestation of uremic intoxication was considered. The necropsy findings threw no light upon this.

Case II

History: On May 2, 1936 there was admitted a white male salesman, aged 46, who for three weeks had been having "cramps" in various muscles, had felt easily fatigued, and had noted loss of energy. Most of his symptoms, however, appeared very suddenly four days preceding admission when he developed a "hard chill," a fever of 104° F., generalized aching and profound malaise. The following morning

he noticed numerous small, sore, red spots scattered in the skin of various parts of his body, but localized chiefly on the extremities. The day preceding admission he developed pain and slight swelling in the knees, ankles and wrists.

He had gonorrhea at the age of 26.

He was told eight years before the present illness that he had a "slightly leaking heart valve."

Physical Examination: On admission he appeared acutely ill. His skin was hot (temperature 103° F.) and he was perspiring freely. Scattered on the distal portions of the extremities, and to a much less extent over the other parts of his body, were numerous circumscribed, purplish-red areas in the skin, varying in diameter from 2 mm. to 1 cm. Some of these were slightly tender. Many showed a central white area of necrosis and a few showed vesiculation with accumulations of seropurulent fluid. No petechiae were present in the mucous membranes. The blood pressure was 145 mm. of mercury systolic and 90 diastolic. The apex beat was in the fifth interspace, 9 cm. from the midsternal line. There were no shocks or thrills over the precordium. There was a moderately loud, blowing, systolic murmur, best heard at the mitral area, transmitted to the left axilla. There were slight swelling and pain about the ankles and wrists. Only slight pain was excited by manipulation of the joints and it was felt that the inflammation was in the periarticular tissues rather than in the joints proper.

Course: His course was that of septic illness with "spiking" temperature chart and occasional chills. The leukocytes ranged from 8,000 to 12,000 per cm. The petechiae gradually faded over a period of four weeks. The swelling about all the joints, except the right ankle, subsided in a few days. During the second week the right ankle became tremendously swollen, exquisitely tender and red. Pus was aspirated from this joint and gonococci were demonstrated by smear and culture. During the second week in the hospital the systolic murmur at the mitral area changed in quality and intensity. It became louder and harsher. No gonococci could be demonstrated from urethral or prostatic excretion, but there were many pus cells. Blood cultures taken on May 2, 4, 8 and 15 yielded no growth. May 4, agglutination tests with *B. typhosus, B. paratyphoid A, B. paratyphoid B, B. melitensis, B. abortus* and *B. proteus X-19* were negative. These agglutinations were repeated May 14 and were again negative. An electrocardiogram, May 4, showed the S–T segment to form the ascending limb of a high peaked, diphasic T-wave in Lead II; S–T segment was of low origin in Lead III. On May 8 the complexes were normal except that T_1 and T_2 were slightly diphasic. On May 19, the complexes were interpreted as being due probably to transient myocardial disease (embolism?).

He was placed in a Kettering hypertherm on May 26. His temperature was maintained between 105 and 106° F. for five hours. Following this treatment his temperature returned to normal and remained practically normal thereafter. There was a marked decrease in the inflammatory reaction about the ankle. It was noted that the mitral murmur was less harsh. On May 29 he was given a second treatment. His temperature was held at between 106 and 107° F. for five hours. The ankle continued to show steady improvement. He was given a third treatment June 2, when, after it had been maintained at 106.5° for two hours, his temperature suddenly rose to 108.2°. The patient developed evidence of impending collapse and treatment was discontinued. June 10 he was discharged free of symptoms, except for slight discomfort in the right ankle.

Six months later the patient reported that he had returned to his work a few weeks after discharge from the hospital. His "follow-up" examination at this time was essentially normal except for the persistence of a faint systolic murmur at the mitral area.

The sudden onset of this patient's illness with a chill and high fever, the presence of numerous large petechiae with areas of central necrosis, the high, septic temperature with occasional chills, the transient multiple arthritis with subsequent development of acute purulent monarticular arthritis from which gonococci were obtained, the presence of transient electrocardiographic alterations indicating acute changes in the myocardium, and the change in character of the apical murmur constitute convincing evidence of severe (metastatic) gonococcal infection and strongly suggest that gonococcal endocarditis was present. Recovery was prompt and complete, following treatment with artificial fever.

Summary

1. A case history of proved and one of probable gonococcal endocarditis treated in the Kettering hypertherm are recorded.

2. In the proved case, fever treatment resulted in sterilization of the blood and, as established at necropsy, sterilization and healing of the endocardial vegetations. Death was due to co-existing syphilitic cirrhosis of the liver and uremia. At autopsy no pathologic changes were noted in the viscera which could be attributed to the effect of fever treatment per se.

3. In the case designated as probable gonococcal endocarditis with co-existing acute gonococcal arthritis, fever treatment resulted in prompt recovery.

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SEVERE BONE-MARROW DEPRESSION FOLLOWING ARSPHENAMINE; REPORT OF TWO CASES WITH RECOVERY *

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The authors delayed reporting the following two cases of arsphenamine bone-marrow depression for several years in order to make certain of the permanency of the recovery which occurred in both cases. The blood dyscrasias occasionally caused by arsphenamine have been reported in the literature mainly under the headings of their outstanding clinical manifestations, such as granulocytopenia, agranulocytosis, thrombocytopenia, or aplastic anemia. A study of these reports and of the two patients who were followed carefully on the wards of Beth Israel Hospital has confirmed our belief that most cases may best be considered as early or late instances of the same toxic process which in its severest form causes complete aplasia of the bone-marrow.

Case Reports

Case 1. L. W., male, aged 50, cloak manufacturer, admitted May 4, 1933 because of weakness, fever, joint pains and frontal headaches of two weeks' duration, and a rash over his lower extremities which had appeared the preceding day.

The patient had a chancre confirmed by dark-field examination in 1918. Antiluetic therapy was begun immediately and continued for two full years. The Wassermann examination was positive only once. After this there were no complaints referable to the disease except for a feeling of numbness and cold in the toes and finger tips for three years before his present illness. Two months before admission (March 1933) following exposure to infection the patient again developed a chancre, also confirmed by dark-field examination, thus providing an excellent example of that rarity—a second chancre. Intravenous therapy was begun and nine injections of salvarsan were given, twice weekly. The last six injections were followed in four to five hours by marked general reactions with chills and fever. The patient felt worse after each reaction, finally taking to bed two weeks before admission because of weakness, lassitude, aching joints, severe frontal headache, and moderate fever. The case was diagnosed as grippe, but the pyrexia and other symptoms failed to disappear. Three days before admission to the hospital, while crossing his left knee over his right, he experienced a sudden click in his left calf; this area became painful and hard, but not reddened. On the day of admission he developed a rash on both lower extremities which did not itch.

Physical Examination: The patient appeared chronically ill, markedly pallid. No lymphadenopathy was present. The pupils were equal, regular and reacted well to light and accommodation. The tongue was not atrophic; the gums were normal; the teeth false. The heart was not enlarged; a soft systolic murmur was heard at the apex. The lungs were emphysematous. The liver was palpable two fingers below the costal margin as a smooth, non-tender mass; the spleen was barely palpable. Knee jerks, ankle jerks and other reflexes were normal. There was no loss of vibration or

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position sense. There were fine petechial hemorrhages (purpuric) over both legs, both arms and in the right axilla. The tourniquet test (Rumple-Leeds phenomenon) was positive. The left calf muscle was hard and tender.

Laboratory Data:

Urine	June 5: Sp. gr. 1.018, acid, amber, very faint trace of albumin, no glucose, no casts, no red blood cells, occasional white blood cells.
	June 8: Arsenic is present.
Feces	June 6: Blood and bile present.
Venous pressure	June 5: 7.5 cm.
Sedimentation rate	June 5: 130 mm. in 45 minutes.
	July 16: 90 mm. in 45 minutes.
Icteric index	June 29: 7.
Wassermann	June 5: Negative.
	June 18: Negative.
Blood culture	June 29: Sterile.
Blood chemistry	June 5: Glucose 133 mg. per cent; non-protein nitrogen 26 mg. per cent.
	July 19: Fibrinogen 2.1 g./100 c.c. plasma.
Culture of pus from thigh	July 18: *Staphylococcus aureus.*
Roentgen-ray of chest	June 8: Shows normal heart, aorta and lungs.
Electrocardiogram	June 9: Sinus tachycardia.

The blood counts and the dates of transfusions are shown in the following table.

Progress Notes: The patient entered with a temperature of 101.2° F., but this rose to 106.2° the next evening, and varied between 102° and 105° for the next week. Intravenous sodium thiosulphate and repeated intramuscular injections of adenine and pentnucleotides in the first two weeks of his stay did not prevent the continued fall of the white blood count from 1900, with 48 per cent polynuclear cells, to 1,350 with 20 per cent polynuclears on the seventh day (June 10) and 1,600 with 32 per cent polynuclears on June 22, when the treatment was stopped.

A bone-marrow puncture over the upper third of the sternum was performed on the third day of his stay (June 6). The marrow was red, but appeared somewhat less cellular than normal. Microscopic examination revealed numerous normoblasts; no megaloblasts; no myeloblasts; many myelocytes, *metamyelocytes* and *staffs*, the latter two predominating. There were few mature segmented neutrophiles. No megakaryocytes were seen. The fact that pathologically the bone-marrow showed no increase in younger cells but an apparent decrease in mature elements ruled out definitely a truly organic aplastic anemia. The most probable diagnosis, considering the normal cellular elements found on biopsy and the neutropenia, thrombocytopenia and anemia shown by the peripheral blood was a toxic inhibition of the bone-marrow due to the arsphenamine. These bone-marrow findings were the rationale for transfusions, which were repeated about twice weekly in spite of failure of the patient's blood to respond to them.

June 17, 1933: The patient showed dryness and desquamation of the skin of the upper extremities, chest and back. The dermatologist considered the skin eruption an arsenical exfoliative dermatitis. There were many new petechiae over the chest, back and mouth at this time.

June 22: There was a small area of beginning ulceration between the hard and soft palate which lasted only a few days.

June 27: Purpuric manifestations were increasing while the white blood count showed a steady rise in polymorphonuclears. For the first time the patient showed

TABLE I

Blood Counts and Transfusions (Case 1)

Date	Erythrocytes	Hgb. %	W.B.C.	Total		Staff.	Seg.	Eos.	Mononuclears		Platelets	Other Findings	Transfusions
				Polynuclear	Mononuclear				Lymphocytes	Monocytes			
6/4	2,290,000	55	1900	48	52	2	46			6	Dimin.	1 normoblast	
6/5	2,000,000	48	2000	23	77	8	14	1	71	6	50,000	slight macrocytosis; toxic degen. of polys.; 1 myelocyte	
6/7	2,360,000	48	1800	11	89	1	8		89	0			300 c.c.
6/9	2,390,000	47	1600	16	84	6	8	2	80	4		slight toxic degen. of polys.; no poikilocytes; no polychrom.	500 c.c.
6/10	2,890,000	56	1350	20	80	7	12		72	8	43,350	aniso.; polychrom.	
6/12	2,960,000	55	1700	18	82	6	12		80	2		aniso.; polychrom.	400 c.c.
6/14	2,660,000	52	2000	20	80	4	16		77	3		aniso.; polychrom.	
6/15													500 c.c.
6/17	2,820,000	56	2050	26	74	9	13	1	62	12		2 plasma cells, 2 myelocytes	
6/19											30,900		500 c.c.
6/22	2,480,000	55	1600	32	68	6	22	3	66	2		1 myelocyte; polychrom.	300 c.c.
6/26	2,600,000	59	1900	39	61	6	20	1	54	7		2 myelocytes	300 c.c.
6/27	3,220,000	61	2500	32	68	9	21		63	5		1 myelocyte	
6/29	2,680,000	60	2000	29	71	7	22	1	60	10		marked degen. of neutrophiles	
6/30													300 c.c.
7/1	2,620,000	51	2400	24	76	4	17		64	12	35,000	2 myelocytes	
7/3													300 c.c.
7/5	2,590,000	52	3400	27	73	5	19	2	59	13		1 myelocyte	
7/7													300 c.c.
7/8	2,630,000	55	2500	39	61								
7/10													300 c.c.
7/12	2,700,000	52	4400	50	50	10	40		37	13		marked aniso.	
7/13	2,670,000	50	5150	42	58	9	33		48	10			
7/14			4300	34	66	9	24		51	15		1 myelocyte	
7/15	2,460,000	45	4300	39	61	7	30	2	54	7			
7/17	2,220,000	46	3200	37	63	8	28	1	52	11		marked aniso.; polychrom.	300 c.c.
7/18											8,880		
7/19	2,520,000	50	3600	44	56	7	36	1	42	14			
7/21	2,540,000	48	4400	44	56	4	40		50	6			300 c.c.
7/24	2,810,000	52	4000	48	52	2	46		47	5			
7/26	3,050,000	54	5000	43	57	4	36	1	52	5			
7/28	3,180,000	58	4000	47	53	4	42	1	45	8			
7/31	3,260,000	59	4600	27	73	2	24	1	69	4			
8/1			4500	36	64	3	30	2	60	4			
8/2			4050	28	72	2	23	3	68	4			
8/3	2,950,000	56	3800	34	66	4	27	4	59	7			300 c.c.
8/4	3,370,000	62	4400	44	56	7	32	4	53	3			
8/7	3,430,000	64	4100	36	64	4	31	1	60	4			
8/9	3,230,000	62	4400	35	65	2	31	2	60	5	9,900		
8/14	3,240,000	62	4550	30	70	2	27	1	65	5			
8/16	3,130,000	60	3600	38	63	1	34	2	57	5		slight macro- and microcytosis	

some clinical improvement. The temperature, which ranged between 101° and 106° F. rectally the first three weeks, sought a lower level (100° to 103° F.) now.

June 29: An erythematous area on the right hip was noticed, with a tendency to pustule formation; this cellulitis became softer and disappeared in about two weeks.

July 11: The hematoma of the left calf muscle, which always had been hard and non-tender, became softer and more tender.

From July 12 on, the blood and clinical picture showed steady improvement (table 1). There was only a sub-febrile temperature at this time, which later became normal. The patient felt a daily increase in strength. Upon his discharge ten and one-half weeks after admission he felt perfectly well except for the painful diffuse swelling of his left calf muscle due to an organized hematoma. His blood count on this day (August 16) was: Red blood cells 3,130,000; hemoglobin 60 per cent; white blood cells 3,600; polymorphonuclears 48 per cent. Discharge Diagnosis: Arsphenamine panmyelophthisis. Arsenical exfoliative dermatitis. Organized hematoma of left calf.

Follow-Up Notes: Patient had no complaints at any time when a follow-up blood count was done. The general condition was good; the heart, lungs, skin and joints negative. Blood counts were as follows:

Date	R.B.C.	Hgb. %	W.B.C.	Polys.	Monos.	Staff.	Eos.	Lymphs.	Monos.
2/ 8/34	4,070,000	69	5,800	46%	54%	3%	3%	50%	4%
9/23/35	3,780,000	86	5,700	53%	47%	1%	4%	42%	5%
1/ 7/36	4,530,000	90	7,100	47%	53%	2%	5%	43%	10%

Comment on Case. The importance of the bone-marrow puncture in this case cannot be overemphasized, for it indicated that, although findings in the peripheral blood were those of an aplastic anemia (granulocytopenia, thrombocytopenia and erythrocytopenia) the bone-marrow was not aplastic. Its function was simply suspended. The biopsy bolstered up our faith in the efficacy of persistent transfusions during the first four weeks when the patient failed to show any clinical improvement, and when his condition appeared hopeless, because of the marked asthenia, hyperpyrexia and bleeding. We believe the repeated transfusions saved this man's life by tiding him over the acute emergency of toxic inhibition of the bone-marrow. It is interesting to note that when the patient's condition began to improve and his blood to show a rise in the polymorphonuclears, the infected areas on the right buttock and left calf became soft, fluctuant and purulent, and showed the more typical picture of an acute infection which is undergoing healing, whereas previously these areas were more indolent and showed no pus. This contrasts with the case of dysplastic granulocytemia reported by Weiss and Goldbloom [1] where clinical improvement in an anal slough did not occur even though leukocytosis (up to 40,000 cells) followed several weeks of granulocytopenia. That patient died in spite of the return of the neutrophiles because these cells, although plentiful in number, were of deficient quality, due to an irreparable injury to the mother-cell. In our present case, however, there was apparently no such injury to the mother-cell, for once

the bone-marrow resumed its hematopoietic function the patient's condition improved rapidly, and was no longer serious. The follow-up blood counts show that the recovery was complete, and there was no tendency to relapse.

Case 2. E. L., male, aged 32, manager, admitted June 19, 1933 with progressive weakness and bleeding from nose and gums for about one month.

The patient discovered he had a four-plus Wassermann in the course of a routine study for a "cyst" near the rectum about six months before. He immediately underwent a course of arsphenamine therapy, receiving an injection once a week for six weeks, until his Wassermann was negative. There were no immediate ill-effects except for mild nausea on the injection days. After this he received seven more injections at three-week intervals. The dosage was rather high (from 0.5 to 0.9 grams). He noticed that he was becoming progressively weaker and that he tired very easily. About three to four weeks before admission he began to bleed from the gums, and later had bleeding from the nose one night. The bleeding from the gums was intermittent, and became much worse five days before admission. Three days before his entry into the hospital his vision, which was failing, became so poor that he could not read the newspaper headlines.

Physical Examination: The patient appeared extremely pale, subicteric, chronically ill. Pupils normal. Fundi rather pale with numerous hemorrhages, mostly along the course of vessels. The tongue was coated, the breath fetid, the gums bleeding. Slight enlargement of the cervical glands was present. The heart and lungs were negative. The liver was palpable at the costal margin; the spleen was not felt. The knee and ankle jerks were obtained on reinforcement. There was no loss of vibration or position sense in the lower extremities.

Laboratory Data:

Average Urine Analysis:	Sp. gr. 1.014, acid, amber, very faint trace of albumin, no glucose, no casts, rare red blood cells, rare white blood cells.
	June 20: Arsenic not present.
Feces	June 24: Blood and bile present.
	June 27: Blood and bile present.
	July 20: Blood present.
	Aug. 23: Blood absent.
Venous pressure	June 19: 6 cm.
Sedimentation rate	June 19: 134 mm. in 45 minutes.
Icteric index	June 21: 7.
Tourniquet test	June 25: Negative.
	July 9: Positive.
Clot retraction	June 27: Normal.
Bleeding time	June 27: Before transfusion) 90 minutes.
	June 29: (After transfusion) 3 minutes.
Coagulation time	June 29: 3.5 minutes.
	Aug. 24: 3 minutes.
Wassermann	June 19: Negative.
Blood chemistry	June 20: Glucose 133 mg. per cent; non-protein nitrogen 35 mg. per cent.
	July 7: Calcium 9.8 mg. per cent; phosphorus 3.0 mg. per cent.
	July 19: Fibrinogen 0.9 g./100 c.c. plasma.
Electrocardiogram	June 20: Sinus tachycardia.
	Aug. 4: Frequent ventricular extrasystoles.

The blood counts and the dates of transfusions are shown in the following table.

Progress Notes: The patient at first was given sodium thiosulphate intravenously for two days and pentnucleotides intramuscularly for five days. This apparently had no effect on the white blood count, which fell to 1150 with 11 per cent polys. on June 24 (table 2), when there was bleeding from the gums which lasted all day. In spite of repeated transfusions the patient's condition remained grave; gingival bleeding persisted; even though it would stop for a period shortly after a transfusion. Transfusions were given bi-weekly; but with little apparent effect on the blood picture. On July 25 the patient's temperature, which had remained about normal after the first week, rose to 104° F. A fissure-in-ano with large hemorrhoids and an ischio-rectal abscess were found to be the cause of the fever. The abscess was incised on July 31, after which time the temperature fell to normal. The wound failed to granulate, however, and by August 11 there was still no evidence of healing. The patient was failing fast. Bleeding from the gums and nose increased, diminishing only slightly for a short period after a transfusion. Surprisingly enough, however, about August 17 and 18 a sudden turn for the better occurred. The wound began to granulate. On August 21 the patient for the first time stated that he felt well. Though there was

TABLE II

Blood Counts and Transfusions (Case 2)

Date	Erythrocytes	Hgb. %	W.B.C.	Total		Staff.	Seg.	Eos.	Mononuclears		Platelets	Other Findings	Transfusions
				Polynuclear	Mononuclear				Lymphocytes	Monocytes			
6/20	1,050,000	23	2300	9	91	5	4		85	6	78,759	reticulocyte 0.2%	500 c.c.
6/23	1,160,000	25	1600	14	86	4	10		80	6	30,900	1 normoblast	
6/24	1,230,000	21	1150	11	89	5	6		85	4			
6/26													500 c.c.
6/27	1,270,000	26	2000	12	88	3	8		86	2	10,900	1 myelocyte	
6/28													500 c.c.
6/29	1,790,000	34	1500	18	82	2	16		82		15,300		
6/30													400 c.c.
7/3	1,800,000	35	1600	26	75	6	18		67	8	16,900	1 normoblast, 1 plasma cell, 1 myelocyte	300 c.c.
7/5	2,190,000	45	1500	24	76	6	18		67	9	13,050		300 c.c.
7/7													300 c.c.
7/8	2,690,000	47	1150	25	75	9	16		63	12		2 plasma cells	
7/9	2,250,000	40											
7/10	1,860,000	38	1960	14	86	3	11		74	11		1 myelocyte, 2 plasma cells	300 c.c.
7/12	2,580,000	42	2650	26	74	5	20	1	69	5		1 plasma cell	
7/13	2,460,000	39	3100	18	84	3	15		80	2			
7/14													300 c.c.
7/15	2,490,000	47	3000	20	80	3	17		73	7			
7/17	2,325,000	48	2700	15	85	4	10	1	69			1 myelocyte	300 c.c.
7/19	2,350,000	46	2050	20	80	7	13		70				
7/21	2,610,000	48	3200	20	80								300 c.c.
7/24	2,750,000	49	2800	18	82	4	14		77	5			300 c.c.
7/26	2,500,000	47	2600	17	83	6	9	1	72	11	7,500	1 normoblast	
7/28	2,250,000	41	2000	9	91	5	4		83	8			300 c.c.
7/31	2,200,000	40	2500	11	89	5	6		80	9			500 c.c.
8/1			3000	53	47	12	41		44	3			
8/2			3200	52	48	16	35	1	46	2			

TABLE II—*Continued*

Date	Erythrocytes	Hgb. %	W.B.C.	Total		Staff.	Seg.	Eos.	Mononuclears		Platelets	Other Findings	Transfusions
				Polynuclear	Mononuclear				Lymphocytes	Monocytes			
8/3	1,810,000	34	2900	60	40	18	42		37	3	8,550		300 c.c.
8/7	1,690,000	34	3250	28	72	8	19		72				
8/8													300 c.c.
8/9	2,010,000	38	3500	33	67	5	28		65	3			
8/10	2,150,000	38	3450	38	62	4	34		59	2			300 c.c.
8/11	2,350,000	40	3650	36	64	7	28		63	1			
8/14	2,230,000	42	3600	40	60	4	34		60				
8/16	2,350,000	44	3450	33	67	5	28		63	7			
8/18	2,400,000	48	3200	41	59	2	37	2	54	5		aniso.; polychrom.	
8/20	2,080,000	42	4050	33	67	4	29		59	8		aniso.; polychrom.	
8/23	2,020,000	41	3600	41	59	4	35		52	7	9,200	aniso.; polychrom.	
8/25	1,890,000	38	3000	39	61	3	35	1	55	6		aniso.; polychrom.	
8/26													300 c.c.
8/27	2,210,000	44	4400	39	61	5	32	2	58	3			
8/28	1,940,000	36	3300	43	57	4	37	1	52	5		aniso.; polychrom.	
8/30	1,870,000	32	3800	47	53	5	51		46	7		macro- and microcytosis	350 c.c.
9/1	1,860,000	39	3600	38	62	4	34		54	8		macro- and microcytosis	350 c.c.
9/2	2,010,000	37	3800	48	52	5	42		46	6	7,400	reticulocytes 0.2%	
9/5	1,890,000	38	4000	40	60	4	35	1	34	6			
9/7	1,900,000	38	4100	46	54	4	41	1	49	5		reticulocytes 1.6%	300 c.c.
9/8	2,590,000	44	3600	49	51	3	43	2	48	3		2 normoblasts, macrocytosis	
9/11	2,221,000	40	3400	49	51	2	45	2	46	5		reticulocytes 0.7%	
9/14	2,340,000	42	3500	38	62	6	32		55	7		1 normoblast	
9/16	1,930,000	42	3900	47	53	5	40	2	42	11	6,400	anisocytosis	
									Follow-up				
1934													
1/20	4,010,000	80	6500	62	38	5	56	1	33	5		platelets normal	
3/14	4,450,000	86	7000	65	35	5	60	0	31	4		platelets normal	

no appreciable change in the white, red, or platelet count the patient was now able to sit up in a chair. On August 25 the red blood count, hemoglobin, and white blood count fell, and three more transfusions were given even though the patient was feeling better and the bleeding from the gums and nose had stopped. On September 16, 1933, thirteen weeks after admission, the patient was discharged with 1,930,000 red blood cells, 42 per cent hemoglobin, 3,990 white blood cells, and 47 per cent polymorphonuclears. Although his blood picture did not show complete recovery by any means, he was clinically much improved. At home his private physician placed him on high doses of iron and ventriculin. With this medication, rest and high caloric diet he rapidly regained his former strength. A blood count taken four months after his discharge was normal in every respect, as were blood counts taken six, eight and ten months later. The patient has remained healthy and normal to date; weighs fully 200 pounds and has no complaints at all.

Comment on Case. This patient unfortunately did not permit a bone-marrow puncture, so that we do not know the true condition of his bone-marrow. Clinically the patient closely resembled the previous case, and we feel that the bone-marrow biopsy, if performed, would have been similar to that of case 1. It is noteworthy that this patient received fully 21 transfusions. The patient's condition at this time was truly desperate. The blood given by transfusion seemed to be lost almost at once. In fact, 17 transfusions were given before any clinical improvement was shown. Transfusions were persisted in since no other rational therapy was available. Looking back we feel that only the repetition of the transfusions enabled us to tide him over the period of bone-marrow inactivity.

Discussion

Up to the present more than 100 cases of depressed bone-marrow function following arsphenamine administration have been reported. Despite the high figure, we must still consider it a rare disease in view of the widespread use of this group of arsenicals in the treatment of syphilis. The rarity of the disease can be explained by the well-established fact that the bone-marrow is more resistant to disease than most other organs and has unusual tissue immunity against infections, toxins and chemical poisons. Where the bone-marrow is depressed by arsphenamine we must assume that it probably is a *locus minoris resistentiae* in the afflicted individual; or that some individual constitutional inferiority makes it unusually susceptible to the toxic action of arsphenamine. Unfortunately, there is no way of determining beforehand this constitutional predisposition; we have no clinical guide-posts which warn us of this type of danger in any individual case before we start the arsphenamine treatment.

A careful study of the literature on the blood dyscrasias after arsphenamine administration and of our own two patients suggests that it is the benzol arrangement in the arsphenamine molecule rather than its arsenic content which is capable of producing effects on the blood forming tissues. In only one case in the literature did signs of bone-marrow depression follow the use of an *inorganic* arsenic compound,[2] so that such bone-marrow effects must be considered a very unusual toxic action of arsenic. On the other hand, there is a striking clinical and hematological similarity between the blood dyscrasias caused by arsphenamine and those which have been observed after industrial poisonings with benzol.

Although Santesson [3] should be credited with the pioneer work on benzol toxicity, in this country it was Selling [4] who first stressed the selective depressant action of benzol on the hematopoietic system. Frank [5] named this type of reaction of bone-marrow to a poisonous substance "panmyelophthisis," a very appropriate term to which we subscribe. It is surprising that it was not until 1919, fully nine years after the introduction and wide-

spread use of arsphenamine, that Labbé and Langlois [6] first warned against the danger of bone-marrow depression following its use, and suggested that the action is possibly due to the benzol constituent of arsphenamine. Since then numerous excellent articles have been written by the many workers in this field, who have confirmed the general tenor of these findings, and have reported the cases which they observed under the title of the leading hematological symptom—neutropenia, purpura, hemorrhagic diathesis, anemia, etc.[7, 8, 9, 10, 11, 12, 13]

The attempt to classify the blood dyscrasias caused by arsphenamine has always been difficult. No classification can be entirely satisfactory and fit all cases. McCarthy and Wilson [13] suggest three main divisions: (1) thrombocytopenic; with subgroup 1 b. thrombocytopenic and granulocytopenic, (2) granulocytopenic and agranulocytic and, (3) aplastic. We are in agreement with the spirit of the first division which differentiates the simple, uncomplicated thrombocytopenic type of reaction from the true bone-marrow depressive type. The reaction in the former is short-lived, readily recovered from. It occurs immediately or shortly after an injection; the blood picture is entirely normal except for the temporary reduction in blood platelets. The simple thrombocytopenic reactions are probably of an "anaphylactoid" nature, as McCarthy and Wilson suggest, and are not considered cases of true bone-marrow depression. With the authors' division of the true bone-marrow depressions according to the outstanding hematological finding, thrombocytopenia, granulocytopenia or complete aplastic anemia we cannot be in such close agreement, for the divisions appear to us to be purely descriptive, and to bring us no closer to the mechanism in these cases.

Considering the probable identity of arsphenamine and benzol bone-marrow depression, we feel that the reported cases can best be viewed and classified as early or late stages of the same process—the early stage consisting essentially of depression of the granulocytes, the later stage including depression of the other elements in the bone-marrow, leading finally to a complete aplastic anemia. The excellent charts of McCarthy and Wilson [13] summarizing the main features of all cases reported up to 1932 bear out this contention. The granulocytopenic cases occur after smaller doses, i.e. have a shorter incubation period, and appear at a shorter interval after the last injection than do the aplastic anemia cases. In the latter cases the arsphenamine has been given over a much longer period, and the reaction occurs weeks to months after the last injection, rather than days; the clinical picture is more serious; the prognosis worse.

The experimental work of Alice Hamilton [14] on benzol poisoning also agrees with the conception of the unity of the depressive process in almost all clinical cases. She demonstrated that several days after the injection of a relatively large dose of benzol in animals the white blood cells were reduced to about 50 per cent of normal. If the same dose is injected again,

the count falls within two or three days to 20 per cent (or even as low as 12 per cent) of normal. If she gave no injection after the first one, the fall in white blood cells would continue to a level well below the 50 per cent, but later there would be spontaneous and complete recovery. However, if the second injection was given, the count would eventually fall below 12 per cent and recovery failed to take place. The myeloblastic elements, particularly the polymorphonuclears, were found depressed by the benzol. There was no destruction of the white blood cells in the circulating blood, but an inhibition of their formation. Only later with increasing doses was a depressive effect on the other tissues in the bone-marrow demonstrated (red blood cells and platelets).

Translated to human subjects, the primary action of benzol (arsphenamine) is depression of granulocyte formation; this action is early, and can be reversed if no more benzol is administered. However, with continued benzol doses, the later " secondary " actions are permitted to develop and an irreversible situation is brought about. The secondary effects are on the megalokaryocytes, causing not only a reduction in number, but also in quality of the platelets. The hemorrhagic diathesis that results leads to bleeding from the gums, nose, gastrointestinal tract, etc. The red blood cells are thus involved secondarily, suffering in proportion to this bleeding. Since benzol does not affect the red blood cells primarily there are no signs of regeneration—no reticulocytes, or nucleated red blood cells.[15] The final, late stage of arsphenamine bone-marrow depression is thus a " panmyelophthisis." If the bone-marrow has simply been depressed, there is some chance of recovery with repeated transfusions that tide the patient over the period of bone-marrow inactivity. Where a true aplasia of the bone-marrow has resulted, however, there appears to be little basis for any such hope. It is not possible to make this differentiation (depression or true aplasia of bone-marrow) from the study of circulating blood alone. It is of the utmost importance prognostically to perform a bone-marrow puncture in these cases. In case 1 a puncture was performed in the first week at the hospital and showed red bone-marrow with about the usual number of young cells, but few mature segmented neutrophiles. This depression without aplasia of the myeloid system indicated that there was some bone-marrow tissue left to stimulate with repeated transfusions. The term " panmyelophthisis " we believe describes the condition of functional depression of the bone-marrow better than " aplastic anemia," a term which indicates organic depletion of the bone-marrow. This condition surely did not exist in case 1, and in all probability was not present in case 2, either.

A few words must be said about the clinical course shown by the two cases reported. " Panmyelophthisis " is a relatively late reaction of the body to arsphenamine poisoning and occurs typically several months after the beginning of arsphenamine administration. The " incubation " period is long here when compared with the toxic effects of arsphenamine on the liver

(where symptoms are likely to appear much earlier,—i.e., during the first few weeks). This may be because the first symptoms of toxic action of arsphenamine on the bone-marrow are slight, there being only signs of general intolerance of the drug, such as the weakness, nausea and feverishness that case 1 experienced after each injection. Moore and Keidel [7] speak of itching or a fine rash as prodromata. The only unmistakable sign of trouble, however, is the neutropenia. It cannot therefore be urged too strongly that patients who show any intolerance of, or reaction to, arsphenamine injection should have a blood count performed. By this means we can detect the neutropenic cases and stop administering the drug before irreversible damage has occurred. Our therapeutic desideratum is to recognize intolerance of the bone-marrow to arsphenamine before a hemorrhagic diathesis or an aplastic anemia has set in. By constant vigilance for the advent of neutropenia, we can recognize these cases early enough to stop the progress of the disease to the fully developed "panmyelophthisis," which, in spite of the best of treatment, is fatal in about 80 per cent of the cases.[13]

At the stage when the disease is confined to the leukoblastic tissues (the first or "neutropenic" stage) the nucleotide administration as sponsored by Jackson [16] may reasonably be given a trial. In the later stages of panmyelophthisis, as in our two cases, nucleotide injection appeared to have no appreciable effect on the white blood cells. The treatment is preferably the use of persistent transfusions until death or recovery supervenes.

Summary and Conclusions

Two cases of complete bone-marrow depression several months after arsphenamine administration are reported. An individual constitutional susceptibility of the bone-marrow to the toxic agent may explain the occurrence of this relatively rare disease. In mode of onset, blood pictures and clinical characteristics such cases resemble very closely those due to chronic benzol poisoning. Although there is no definite proof, it is likely that the benzol ring into which the arsenic is substituted in arsphenamine is responsible for the blood dyscrasias here described, and not the arsenic. The relatively benign hemorrhagic diathesis occurring shortly after an injection of arsphenamine due to an "anaphylactoid" reaction of the thrombocytes is differentiated from the true depression of the bone-marrow caused by the slow accumulation of the toxin (benzol) and resulting in bone-marrow depression weeks and months after the administration began. A study of bone-marrow depression in chronic benzol poisoning, and after arsphenamine administration indicates that the toxin most often shows an early affinity for the leukoblastic tissue in the bone-marrow. Thus, the early, easily reversible action of arsphenamine on the hematopoietic system is most often a reduction in the white blood cells, particularly the polymorphonuclears. Clinically this is expressed as a neutropenia associated with signs of lowered resistance—weakness, persistent colds, numerous smaller infec-

tions, etc. If this early neutropenic stage is recognized and the arsphenamine administration stopped, the patient may be spared the later and frequently irreversible effects on the bone-marrow of the accumulating arsphenamine (benzol).

Reduction in the number and quality of the platelets, with consequent bleeding from the mucous membranes of the nose, mouth, gastrointestinal tract, etc. is more likely to be a later than an early effect. The bleeding alone explains the marked secondary anemia that finally occurs in most cases, although a direct depression of the erythroblastic tissues may be the cause of the erythrocytopenia in some. Thus the final, often irreversible, stage of the toxic action of arsphenamine (benzol) is a depression to a varying degree of all the elements of the bone-marrow. If puncture reveals a bone-marrow which is not aplastic, blood transfusions persisted in for many weeks may tide the patient over the period of temporary marrow inactivity, and lead to permanent recovery, as in the two cases reported. If a true aplasia of the bone-marrow has already resulted, however, the outlook is practically hopeless. The prognostic importance of bone-marrow puncture in this connection cannot be overemphasized. In any case, persistently repeated transfusions, no matter how ill the patient appears clinically, offer the only hope at this late stage of the disease, and are, therefore, always indicated in its treatment.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

BACILLUS FRIEDLANDER INFECTIONS *

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IN the minds of most physicians and in almost all textbooks on bacteriology and clinical medicine, *B. friedlander* [1] is associated with pneumonia and other infections of the respiratory tract. This traditional viewpoint is responsible for the fact that its common synonyms are *Bacillus pneumoniae* and *Pneumobacillus* and that its modern scientific designation according to the Bergey [2] bacteriological nomenclature is *Klebsiella pneumoniae*. Infections of other parts of the body with this organism are generally regarded as relatively less common.

Our bacteriological experience with 198 *B. friedlander* infections is recorded because it contradicts this conception of the predominant rôle played by the organism in infections of various parts of the body. The observations to be reported in this paper, and a critical review of medical literature of the past 75 years, demonstrate that the respiratory tract and especially the lung is actually one of the less common sites of primary infection and that the current terminology serves to perpetuate a wrong emphasis concerning the usual portal of entry and the essential rôle of the organism in infections.

Friedländer discovered his encapsulated gram-negative bacillus in 1882 in spreads made post mortem from the lungs of eight patients who had died of pneumonia. For some four years thereafter it was generally regarded as the cause of pneumonia, until Weichselbaum's [3] report upon the *Diplococcus pneumoniae* in 1886. Although Weichselbaum's observations upon 129 cases established the pneumococcus as the cause of lobar pneumonia, and minimized the relative importance of *B. friedlander*, he observed the bacillus in microscopic spread in nine cases, isolated it in mixed cultures in six and in pure culture in three instances. He and Netter [4] are widely quoted as accepting it as a less frequent cause of lobar pneumonia and bronchopneumonia because they found it in 7 or 8 per cent of their cases. It seems to have escaped notice that their observations as well as the reports of subsequent observers who confirmed their statistics were based upon postmortem bacteriology and, judged by more modern standards, are therefore of doubtful value. Bacteriological experiences reported on large numbers of cases during and subsequent to the World War indicate that *B. friedlander* is encountered relatively rarely in pneumonia.

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Many authentic Friedländer bacillus infections of the lungs and other parts of the respiratory tract have been recorded in the literature, but in most instances it is obvious that the observer is reporting what is undoubtedly a rarity in his experience. Unfortunately, some of the recorded cases are unconvincing because they are based solely upon postmortem culture of the organism from a pneumonic lung or other tissue. Some represent influenzal pneumonia with a secondary invasion with *B. friedlander*. Others are chronic lung abscesses with mixed infections, or tuberculous cavitations with secondary *B. friedlander* infections. Still other cases are metastatic lung abscesses from a primary focus of infection within the abdomen. A case of lobar pneumonia recently reported by Bensley [5] seems to us to have been due to pneumococcus type II and the *B. friedlander* invaded the blood stream only preagonally. Two of the largest and best described groups of *B. friedlander* pneumonia were reported recently by Solomon [6] from Bellevue Hospital and by Bullowa [7] from the Harlem Hospital, New York.

It is beyond the scope of this paper to review the voluminous literature upon this organism, except to state that it has been found in almost every part of the body. Yet almost every textbook of bacteriology and clinical medicine continues to lay stress upon its relationship to pneumonia and most of them state specifically that it may cause a severe, often fatal, but rather rare form of the disease. They usually mention some of the other sites of infection (Zinnser,[8] Jordan,[9] Park, Williams and Krumwiede,[10] Topley and Wilson,[11] British Medical Research Council,[12] Ford,[13] Stitt,[14] Zinnser and Bayne-Jones [15]).

In this paper we have preferred to call the organism *B. friedlander* in preference to the synonyms which associate it with pneumonia and to such descriptive designations as *Bacillus mucosus capsulatus* and, for a subgroup, *Bacillus acidi lactici*. Formerly we did not attempt to differentiate between the various types of Friedländer organisms because of the lack of clear cut bacteriological criteria. More recently Julianelle [16] has divided the *B. friedlander* into three groups, A, B, and C, according to their serologic reactions. Some of the strains were identified serologically by cross agglutination with pneumococcus type II serum (Avery, Heidelberger, and Goebel [17]). The classification by Julianelle is being followed closely in our laboratory, but sufficient information is not yet available regarding the pathogenicity of the various types. For this reason, gram-negative bacilli showing well defined capsules and typical "gum drop" and stringy colonies on solid media were considered to belong to the *B. friedlander* group, provided these characteristics persisted for at least 3 to 4 passages through artificial media. It should therefore be understood that the term *B. friedlander* employed in this report implies the Friedländer group of encapsulated gram-negative bacilli.

Respiratory Tract

The presence of *B. friedlander* in stained spreads made from the sputum or the lung of a patient with pneumonia probably rarely escapes detection. Because of the traditional association of this gram-negative bacillus with pneumonia, its observation anywhere in the respiratory tract usually results in its prompt identification by means of the capsule stain.

On the other hand, so strong is the influence of medical tradition that gram-negative bacilli encountered in the intestinal tract or in the biliary or urinary passages are apt to be associated with the colon-typhoid group of bacteria and to be inoculated for identification upon the various sugar media. Unfortunately, many strains of *B. friedlander* and of *B. coli* form acid and gas in identical sugar media. Unless a capsule stain is made or attention is attracted by the mucoid character of the surface growth on solid media, observations upon sugar media may result in confusing the organism with the colon group. We can conceive of no better explanation for the conspicuous attention which *B. friedlander* continues to receive in bacteriological observation upon respiratory tract infections and the relative neglect of the more important rôle played by this organism in infections of the abdominal cavity.

In reporting cases of primary *B. friedlander* pneumonia, it is important to exclude the following:

1. Secondary invasions (often preagonal) in cases of primary pneumococcus pneumonia.

2. Influenzal pneumonia with secondary invasion of the affected lung by *B. friedlander* and a variety of other organisms.

3. Chronic bronchiectases, lung abscesses and tuberculous cavitations in which a secondary *B. friedlander* infection has occurred.

4. Metastatic infections of the lung from a primary focus of *B. friedlander* infection within the abdomen.

In the authentic cases of *B. friedlander* pneumonia, the cut surface of the consolidated lung may appear peculiarly mucoid. Microscopically, the exudate in the alveoli presents a more mucinous appearance than the usual pneumonic lung and may contain large numbers of encapsulated gram-negative bacilli. The organisms may also be present in large numbers in the interalveolar capillaries.

Table I

Bacillus Friedlander Infections

198 Cases

Site	Number of Cases	Mortality	Bacteremia No.	Bacteremia Died
Gastrointestinal tract	61		1	1
Genito-urinary tract	50	8 (16%)	6	3
Biliary passages and liver	46	14 (30%)	6	5
Lungs and upper respiratory tract	25		1	1
Miscellaneous: skin, meninges, etc.	10		1	1
Vagina, uterus and adnexa	6		1	1

In our series of 198 infections, we have had only two cases of pneumonia in which the clinical and bacteriological evidence during life left no doubt that *B. friedlander* was the primary cause of the pulmonary infection. The rarity of primary Friedländer pneumonias is indicated by the fact that these are the only two proved cases observed at the Mount Sinai Hospital, New York, during a period of 36 years. In seven other cases of lobar or bronchopneumonia, *B. friedlander* was recovered from the sputum or lung during life in association with pneumococci or streptococci.

The organism was also recovered occasionally from pneumonic lungs at necropsy in association with other bacteria, usually pneumococci or streptococci. It may therefore have been a secondary invader or a postmortem contamination. Our experience leads us to believe that *B. friedlander* may at times gain entrance into the body preagonally from the intestinal tract. Postmortem spreads and cultures from pneumonic lungs are therefore of little value.

Other Infections of the Respiratory Tract. Aside from the nine cases of pneumonia, of which only two are primary infections, the organism was isolated 16 times from other infections of the respiratory tract during life. The cases were as follows:

Pharyngitis	1	
Acute otitis media and mastoiditis	3	
Chronic otitis media	1	
Suppurative sinusitis	3	(one with meningitis)
Thornwald abscess of the nasopharynx	1	
Infected thyroglossal cyst	1	
Submental abscess	1	
Pleural effusion of cardiac origin	1	(contamination)
Pleurisy with effusion	1	(probably a contamination)
Chronic lung abscess	1	
Empyema thoracis	2	(one probably a contamination)

One of the cases of mastoiditis developed a *B. friedlander* meningitis and a bacteremia.

The nine cases in which the organism was isolated from an infection in the nasopharynx, the sinuses or the ears contrast numerically with the 163 *B. friedlander* infections of the abdomen, of which 61 were due to perforative lesions of the intestines.

The organism is occasionally encountered in the normal flora of the upper respiratory tract and is undoubtedly responsible at times for infections in the sinuses and the ears. Because of the much greater frequency of its occurrence in the intestinal tract, our experience inclines us to regard its occasional presence in the upper respiratory tract with suspicion as a possible contamination, or as a secondary invader. Even when found repeatedly in pure culture from infected sinuses or ears, it may have been introduced by previous instrumentation.

Dr. Lee Hurd [18] has recently called attention to the fact that 25 years ago *B. friedlander* infections of the upper respiratory tract, the sinuses and the ears were not such rarities as they are today. Comparative statistics of

25 years ago and of today reveal a striking diminution in the frequency of this type of infection. The use by many of the pioneer specialists of unsterile instruments with unsterile hands may possibly have been the means of causing secondary infections of the ear, nose and throat by the introduction of *B. friedlander* and other organisms derived from the intestinal flora. Since the universal introduction of modern aseptic technic into otolaryngo-office practice, these bacteria are rarely encountered in infections of the upper respiratory tract.

The occurrence of *B. friedlander* in ozaena and rhinoscleroma is now generally regarded as a secondary invasion of no causal significance. We venture to suggest that the organism has been introduced in these cases from the intestinal tract by nose picking, a habit almost irresistible in this type of nasal trouble.

Intestinal Tract

B. friedlander is commonly found in the intestinal tract. It has been isolated from the stool in some cases of enteritis (Berthelot and Bertrand,[19] Jampolis, Howell, Calvin and Leventhal,[20] Abel,[21] Zinnser [8]). We have made no systematic effort to determine the frequency of the encapsulated gram-negative bacilli in the intestinal flora, but Dudgeon [22] has found it in the feces of 5.5 per cent of normal and abnormal individuals. Kendall [23] regards *B. friedlander* as an almost constant habitant of the intestinal tract of nurslings, common in the intestinal contents of bottle fed infants and frequently present in small numbers in the adult intestinal tract.

It is, therefore, not surprising that we encountered the Friedländer bacillus most frequently in infections arising primarily from the intestinal tract. In most instances the intraabdominal infection was due to a perforative lesion of the intestine or the appendix. We are able to report 61 cases of this type. The number was limited only by the fact that cultures were usually omitted by the surgeons in intraabdominal suppurations due to perforations of the appendix or other parts of the intestinal tract.

Of the 61 instances in which the intraabdominal suppuration was apparently due to this organism, 53 were appendicitis abscesses. In 16 instances, it was associated with one or more other organisms characteristic of the intestinal flora, most frequently *B. coli.* The organism was also recovered in subphrenic collections of pus and in peritonitis of appendiceal origin, peritonitis complicating an intestinal obstruction, peritonitis due to a perforating carcinoma of the cecum, pelvic abscess secondary to a sigmoid diverticulitis with vesico-sigmoid fistula and perirectal abscess. In spite of the irregularity with which cultures were made in abdominal infections of intestinal origin, our experience indicates that *B. friedlander* is far more commonly encountered in infections arising from perforative lesions of the intestinal tract, particularly the appendix and large intestine, than in infections of any other organ.

Biliary Tract

Cholecystitis and Cholangitis. Friedländer infections of the gall-bladder and bile passages and liver abscess due to this organism have been recorded by Carnot, Dumont and Lebert,[24] Brouardel,[25] Hegler and Nathan [26] and others. In contrast to the relative rarity of respiratory tract infections due to *B. friedlander,* we are able to report 46 cases of suppurative infections of the biliary tract. The pus in the infected gall-bladder or common duct is usually thin and presents no distinctive characteristics. In some instances it is thick and mucoid and has a faint foul odor. Gangrene of the gall-bladder wall and pericholecystic abscesses are observed as in other types of infection.

B. friedlander was present in the pus in pure culture in 43 of the 46 cases of cholecystitis and cholangitis. In two instances it was associated with *B. coli* and in one with *B. coli* and *B. proteus.*

Mechanical Predisposing Causes. Gall stones were present in the gall-bladder or common bile duct in 38 of the 46 cases. In two other instances, the common or cystic duct was obstructed by carcinoma. It is of interest to note that *B. friedlander* infection of the gall-bladder or biliary passages occurred without any obvious predisposing cause only in six cases in the entire series. This suggests that the excretion of the organism by the liver, whenever it gains entry into the portal circulation, is usually accompanied by little danger of infection of the biliary passages—unless there is biliary stasis due to a mechanical cause such as calculus or neoplasm.

Mortality. Our observations reveal a strikingly high mortality for biliary tract infections with this organism. Fourteen of the series of 46 patients died, a mortality of 30 per cent. This extremely high mortality was due in part to the unusually frequent occurrence of cholangitic and pylephlebitic liver abscesses, secondary to the infection of the gall-bladder or biliary passages.

Liver Abscess. In 10 of the 14 fatal cases one or more liver abscesses were revealed by operation or necropsy. In four, the liver abscesses were due to an ascending suppurative cholangitis. Two were produced by direct extension from the infected gall-bladder or the associated pericholecystic abscesses. Four were of pylephlebitic origin. The suppurative pylephlebitis arose in three of the cases as a result of the suppuration in the gall-bladder and common bile duct. In one case, a pylephlebitic liver abscess was secondary to an acute gangrenous appendicitis. Except for this one instance, all cases of liver abscess due to *B. friedlander* developed as a result of a primary infection in the gall-bladder or biliary passages.

In five of the 10 cases, the liver suppuration gave rise to a bacteremia, a remarkably high incidence. In three of these cases, necropsy revealed that the organisms had gained access to the blood stream because of a secondary suppurative phlebitis of an hepatic vein adjacent to the abscess.

Metastatic Lung Abscesses. Multiple lung abscesses were present as a

complication in three of the cases complicated by liver abscess, in two of which the blood culture was positive. One of the cases of metastatic lung abscess developed an empyema of the pleura which required thoracotomy. In a case of suppurative pylephlebitis of the right portal vein and subphrenic abscess a pleural effusion developed in the right pleural cavity, which became infected only after transpleural aspiration of the subphrenic abscess. Thereafter, a pure culture of *B. friedlander* was obtained from the pleural cavity.

When *B. friedlander* is cultured from a lung abscess or an empyema of the pleura, the possibility must be considered that the abscess of the lung or pleura may be metastatic from a primary suppuration of the liver.

Urinary Tract

The organism has been repeatedly described as the cause of infections of the genito-urinary tract (Chiari,[27] Park, Williams and Krumwiede,[10] Villiere,[28] Bertrand-Fontaine and Parlier,[29] Montt-Saavedro,[30] Howard,[31] Macaigne,[32] Speck,[33] Halban[34]). In our experience the *B. friedlander* infections of the genito-urinary tract are somewhat more frequent than those of the gall-bladder, liver and biliary passages. We are able to report upon 50 infections of the urinary tract, compared with 46 cases of infection of the biliary tract. Although the *B. friedlander* is usually found in the liver and biliary tract infections in pure culture, it is more commonly observed in the infections of the kidney and the urinary passages in association with *B. coli, B. alkaligenes, B. pyocyaneus,* or the enterococcus. Like *B. friedlander,* they are derived primarily from the intestinal flora. Mixed infections with one or more of these organisms were present in 13 of the 50 cases. In one of the cases the blood as well as the urine contained both *B. coli* and *B. friedlander.*

Table II

Mechanical Obstruction as a Predisposing Factor in Excretory Infections with *B. friedlander*

Biliary passages and liver	Total number of cases: 46
Stones in common duct or gall-bladder	38
Neoplasm obstructing common duct	2
No obstruction	6
Urinary tract	Total number of cases: 50
Stones in urinary tract	37
Obstruction due to carcinoma of the bladder	1
Obstruction due to adenoma of the prostate	2
Mixed infection in tuberculosis of kidney	2
Horseshoe kidney	1
Kinking of uretero-pelvic junction	1
No obstruction	6

Predisposing Causes. As in the biliary infections, mechanical stasis in the urinary passages was a common predisposing factor, being present in 44 of the 50 cases. Although in the biliary tract the cause of stasis was either calculi or neoplasm, in the urinary tract infections a greater variety of mechanical causes played a rôle. Urinary calculi were by far the most com-

mon contributory cause, but other factors were carcinoma of the bladder in one case, adenoma of the prostate in two, tuberculosis in two, horse shoe kidney in one and kinking of the uretero-pelvic junction in one case. Apparently the organism is excreted by the kidneys whenever it gains entry into the systemic circulation, but even under these circumstances it is not apt to cause an infection in the urinary passages unless there is urinary stasis due to a mechanical obstruction.

Mortality. The mortality rate of *B. friedlander* infections of the urinary tract is lower than that of similar infections of the liver and the biliary passages. Eight of the 50 patients died of the infection, a mortality of 17 per cent, compared with a death rate of 30 per cent in our biliary series. In three of the eight patients who died, the blood culture was positive during life. However, two patients recovered who had a single positive blood culture during the course of their urinary infection and a third patient recovered although blood culture had been positive on two occasions.

Female Genital Tract

Uterine and tubal infections with this bacterium have been reported by Scheyer [35] and Howard [31] and cases of postabortive sepsis by Reichert.[36] Our experience is limited to five cases of suppurative salpingitis or salpingo-oöphoritis complicated by pelvic abscess from which a pure culture of the organism was recovered, and to one case of recto-vaginal fistula following colpotomy. It is reasonable to believe that the infection in some of these cases spread to the uterus and adnexa from the adjacent rectum or colon. In one case of postabortive infection, the organism was probably introduced during instrumentation by contamination with fecal material.

B. friedlander Bacteremias

The literature contains many reports of cases of Friedländer bacteremia (Lenhartz,[37] Canon,[38] Clairmount,[39] Chiari,[27] Conradi,[40] Caussade, Joltrain and Surmount,[41] Beco,[42] Apelt,[43] Wehrsig,[44] Mason and Beattie,[45] Colombe,[46] Lereboullet and Denoyelle,[47] Lereboullet and Pierrot,[48] Breitkoff,[49] Sisson and Thompson,[50] Belk [51]). In Hegler and Nathan's [26] and Courmount, Dujol and Devic's [52] cases, the portal of entry was an infection of the gall-bladder or bile passages, in Chiari's [27] case an ascending suppurative nephritis, in Conradi's [40] an umbilical vein infection and in one of Lereboullet's [48] three cases we suspect the urinary tract. In some of the reported cases, the portal of entry for the bacteremia was not ascertained during life (Abel [21]).

Libman [53] obtained positive blood cultures only three times among over 40 cases of suppurative pylephlebitis and in one of the three instances, the bacteremia was due to *B. friedlander*. On the other hand, the organisms which he encountered most commonly in the blood stream in cases of pyelo-

nephritis arising without any antecedent manipulation in the genito-urinary tract were the colon bacillus and the Friedlander bacillus. He emphasized the fact that the latter is at times mistaken for the colon bacillus, because a proper capsule stain necessary for its identification is not employed.

Cases of *B. friedlander* bacteremia with recovery have been described by Courmont, Savy and Charlet,[54] Mitchell [55] and others. Crohn [56] reported a case of acute *B. friedlander* endocarditis, the portal of entry being a pyelitis, and Schoeppler [57] described a case of pericarditis.

We can report 16 cases of *B. friedlander* bacteremia, of which four recovered. A fifth case recovered from the bacteremia only to return to the hospital subsequently with a secondary (*B. friedlander*) osteomyelitis of a vertebra from which he died. In 14 cases the organism was present in the blood during life in pure culture, in one it was associated in the blood with *B. coli* and in another with several intestinal bacteria.

Portals of Entry. Of the 16 cases of *B. friedlander* bacteremia, six are from infections of the liver and biliary tract, six from infections of the urinary tract, one from an acute otitis media complicated by mastoiditis and suppurative meningitis, one from a postoperative meningitis probably due to fecal or skin contamination during convalescence from an operation for spinal cord neoplasm and one from an infection of the gynecological tract.

In one other case, the organism was recovered in a blood culture from a patient with aplastic anemia only two and a half days before death. The blood culture also contained colonies of *Staphylococcus albus* and *Streptococcus alpha* so that we are probably justified in concluding that this case represented a preagonal blood invasion in a patient dying slowly of a wasting and debilitating disease.

It is of particular interest to note that no case of bacteremia in our entire series had its origin in a primary lung infection and only one in the upper respiratory tract (otitis and mastoiditis). However, others have reported instances of *B. friedlander* bacteremia complicating pneumonia.

In the case of bacteremia which followed an ear infection, there was doubt (1) whether *B. friedlander* had gained access to the ear as a result of an acute nasopharyngitis and sinusitis, or (2) whether some other organism has been the primary infective agent in the otitis and the *B. friedlander* had been introduced secondarily at the time of the myringotomy, 10 days after the onset of the otitis. The mastoiditis developed four days after the myringotomy. Signs of meningitis began almost four weeks later and the patient died of this cause within another week.

Bacteremia Complicating Liver and Biliary Tract Infections

Six cases of bacteremia were observed among 46 *B. friedlander* infections of the liver and biliary passages. Five died of the infection. One recovered and was reported to be well four months after discharge from the hospital.

It is important to note that multiple abscesses of the liver were found at necropsy in all five of the fatal cases. In two the liver abscesses were pylephlebitic and in the other three cholangitic or cholecystic in origin. In the patient who recovered, the liver at operation seemed clinically to be normal. A cholecystitis and cholangitis was found and drainage of the gall-bladder was followed by recovery from the blood stream infection.

In three of the six cases of liver abscess with bacteremia, the organism gained access to the general circulation only after the development of a suppurative thrombophlebitis of adjacent hepatic veins.

In all six cases of bacteremia complicating liver and biliary tract infections, the organism was excreted by the kidneys and could be recovered from the urine. Five developed secondary excretory Friedländer infections of the urinary tract.

Bacteremia Complicating Infections of the Urinary Tract

In our experience, bacteremia due to *B. friedlander* arises as frequently from infections of the kidney and urinary passages as from the biliary tract. This complication occurred in six of our 50 cases of *B. friedlander* infections of the kidneys or urinary passages.

Fortunately, blood invasions from this source are often transient, so that three of our six cases recovered. In two of the recovered cases, the organism was recovered from the blood stream only on the day following a so-called urethral or ureteral chill.

In one of the three fatal *B. friedlander* bacteremias of renal origin, the blood stream infection cleared up spontaneously so that the patient was discharged from the hospital apparently cured. This is the patient previously mentioned who returned eight weeks later because of a metastatic osteomyelitis of a vertebra and died of a secondary *B. friedlander* bacteremia from this source.

Bacteremia from Intestinal Tract Infections

In spite of the fact that the *B. friedlander* is a normal habitant of the intestinal tract and that it is found most commonly in pyogenic infections of the abdominal cavity due to perforative lesions of the intestines and appendix, it rarely enters the blood stream from this site. In one instance in our experience, which we have already mentioned, it entered the blood stream preagonally two and a half days before death in a patient dying of aplastic anemia.

Summary

The Friedländer group of encapsulated gram-negative bacilli usually gain entry into the body from the intestinal tract. For this reason they are frequently encountered in abdominal suppurations due to perforative lesions of the appendix and the colon.

Like *B. coli* and other intestinal saprophytes *B. friedlander* may enter the systemic or the portal circulation and be excreted by the kidneys or the liver. Under these circumstances, excretory infections are apt to occur if there is stasis of urine or bile due to the presence of a calculus, a neoplasm or other mechanical factor. A predisposing mechanical factor was present in 84 of the 96 cases of excretory infections of the urinary and the biliary passages.

The mortality of *B. friedlander* infections of the abdominal viscera is high. There were eight deaths among 50 urinary tract infections (16 per cent) and 14 deaths among 46 infections of the biliary tract (30 per cent). The isolation of *B. friedlander*, especially from infected bile, is therefore of grave prognostic import.

In urinary tract infections, *B. friedlander* is often associated with *B. coli*, *B. proteus*, *B. pyocyaneus*, enterococcus or other bacteria belonging to the intestinal flora. In biliary infections this association is uncommon and the organism is usually recovered in pure culture.

B. friedlander is encountered infrequently in infections of the vagina, uterus and female adnexa, to which it may gain access by direct extension or by lymphatic or hematogenous carriage from the intestinal tract. In some instances it is probably introduced as a contamination from the adjacent rectum or anus by instrumentation or during self induction of abortion.

Primary *B. friedlander* infections of the lungs and the upper respiratory tract are clinical rarities, in comparison with the frequency of infections of the abdominal viscera.

Sixteen cases of *B. friedlander* bacteremia are reported, of which 12 developed from infections of the biliary or the urinary tract. Most of the cases of bacteremia which arose from extrarenal sites of infection developed a secondary excretory infection of the urinary tract during their clinical course. Recovery was common in the bacteremias of renal origin, and unusual in blood infections arising from the liver and biliary tract and other extrarenal sites.

Conclusions

This report of 198 *B. friedlander* infections indicates that the organism is predominantly associated with abdominal infections, especially suppurations due to perforations of the appendix and colon, and next most frequently with excretory infections of the biliary and the urinary tract. In this respect it conforms pathogenically with *B. coli* and other gram-negative bacilli of the intestinal flora. In comparison with the frequency of Friedländer infections of the abdominal viscera, infections of the respiratory tract with this organism are relatively uncommon.

It is therefore recommended that the terms *Bacillus pneumoniae* and *Pneumobacillus* be abandoned because they have served to perpetuate a

wrong conception of the essential rôle of the bacillus of Friedländer in infections, and that the bacteriological designation *Klebsiella pneumoniae* be changed to *Klebsiella Friedlanderi.*

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THE BLOOD PRESSURE IN STENOSIS AT THE ISTHMUS (COARCTATION) OF THE AORTA; CASE REPORTS *

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IT is well known that the arterial pressure in the arms in cases of congenital stenosis at the isthmus of the aorta is frequently higher than the normal. This is so often the case, that the impression is more or less current that hypertension in the arms is a necessary part of the diagnostic picture, and that investigation of all cases of hypertension will lead to recognition of all cases of isthmus stenosis. Gossage [34] has said: "No doubt in these cases the blood pressure is always high, so as to overcome the difficulty of getting the blood through the narrow arterial channels." Lewis,[57] referring to instances of slight constriction and to cases of coarctation complicated by cardiac embarrassment, is of the opinion that "if we note these cases as natural exceptions then it is true to state that most cases, perhaps all uncomplicated cases, of coarctation of the aorta of the adult type present high blood pressure; the statement applies to both systolic and to so-called diastolic readings."

That such views are in accord with the facts in a large proportion of the cases is readily demonstrated. My own experience is perhaps rather typical: of 12 original cases which I have examined, there was an absolute hypertension in the arms in 10; the pressure was not determined in one, while in another it was normal (last case in the series herewith reported). The occasional occurrence of such findings as those in case 5, in which the pressure in the arms, while higher than that in the legs, is nevertheless within normal limits, together with some interesting findings among the cases already reported, will suggest a modification of the general opinion that the finding of hypertension affords the most important clue to isthmus stenosis.

In order to determine the significance and relative incidence of normal blood pressure in coarctation, I have reviewed the literature and have analyzed all the pressure readings that are accessible. With this analysis, I shall report briefly five heretofore unreported cases, including that of the patient with normal pressure.

The first blood pressure readings in this condition seem to have been made by Potain and Bureau [78] in 1892, followed in 1893 by an observation by Steiner.[91] At the present time 170 such reports have been found.

Blood pressure reports divide themselves into four general categories. The first group consists of those cases in which hypertension was demon-

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strated in both arms; the second group contains cases in which hypertension was reported but in which the pressure was determined from one arm only. Doubtless a number of cases of this type would have been found to have elevated pressure in both arms, had a more complete report been given, hence would have appeared in table 1. However, there is a group (table 4) in which there was a hypertension in the right arm, with normal pressure in the left: because of the possibility that some cases in table 2 might have been of the same type as the cases in table 4 or table 1 if the pressure had been determined in both arms, it seems safer to leave all cases of unilateral pressure reports in a separate group (II).

Tables 1 and 2 consist of cases with the more orthodox pressure findings —a definite hypertension in one or both arms and comparatively low pressure with feeble pulsations in the legs.

Of the adult hypertensive patients in table 1 the average pressure in the right arm was found to be 190 systolic and 92 diastolic, that in the left arm 185 systolic and 94 diastolic. Such a difference has been noted in previous reports and has been thought to be due to slowing of the blood stream as it passes the mouth of the left subclavian artery, a condition due to the proximity of the coarctation to the left subclavian. The average pressures in the legs were not unlike, being 125 systolic and 93 diastolic in the right, 120 systolic and 89 diastolic in the left (table 1).

In table 4 is found a group of cases of unusual interest inasmuch as there is a marked disparity of pressure in the two arms, that of the left being within normal limits. This statement should be qualified by pointing out that there was a diastolic hypertension in the left arm in four of the 10 cases of table 4. Moreover, the case reported by East [21] (number 5) is an exception to all rules, since the pressure is substantially higher in the left arm than in the right. As there was no autopsy, the explanation of this bizarre finding is not known.

A possible interpretation of the other nine cases of table 4 is suggested by Parkes-Weber and Knop [71] in discussing the case of Turkington [99] (number 8 in this group). These authors quote D. E. Bedford, who described a case in the Museum of the Heart Hospital, London, in which there was observed a fibrotic stenosis at the origin of the left subclavian artery.

It seems probable that the cases in table 4, excepting that of East [21] (number 5), had an isthmus stenosis complicated by involvement of the mouth of the left subclavian artery in a stenosing process. In cases of "persistent isthmus" the mouth of the artery and the isthmus might well be involved in a single anomaly.

The cases in table 3 deserve especial note, as here are 19 cases in which the arm pressure was within normal limits. I have included my own observation (case 5 in the appended series). Nine cases were substantiated by autopsy. It should be stated that no note was found in some of

CASES OF COARCTATION OF THE AORTA FROM 1892 TO 1936, WITH BLOOD PRESSURE READINGS

TABLE I

Blood Pressure 140 (S) or More in Each Arm

No.	Author	Sex	Age	Blood Pressure		Color	Autopsy
				Arm	Leg		
1.	Baker, T. W. and Shelden, W. D.	F.	25	R. 182/82. L. 176/74.	R. pop. 118/– L. pop. 128/–	W.	No
2.	Blackford, L. M.	M.	30	R. 200/110; 158/100 L. 180/–	R. 120/– L. 135/–	W.	No
3.	Blackford, L. M.	M.	16	R. 164/56 L. 162/62	R. 80/60	W.	No
4.	Blackford, L. M.	M.	16	R. 180/100; 160/76 L. 165/100; 156/82	R. 108/60	W.	No
5.	Blackford, L. M.	M.	46	R. 158/96 L. 154/98	R. 102/80 L. 106/88	W.	No
6.	Blackford, L. M.	F.	16	R. $\frac{180}{86}$; $\frac{206}{90}$; $\frac{176}{104}$ L. 172/102	R. 90/60	W.	No
7.	Blackford, L. M.	F.	22	R. 168/94 L. 164/90	R. 102/88 L. 98/84	W.	No
8.	Brown, J. W.	F.	30	R. 180/20 L. 150/20	100/–	W.	Yes
9.	Carnett, J. B. and Howell, J. C.	M.	75	R. 180/80 L. 160/80	R. 140/96 L. 100/80	W.	No
10.	Codvelle and Henri	M.	21	R. 230/120 L. 230/120	R. 120/90 L. 120/90	W.	No
11.	Eppinger, E. C. and Midelfart, P. A. H.	M.	33	R. 150/80 L. 154/90	R. pop. 122/94 L. pop. 120/90	W.	No
12.	Eppinger, E. C. and Midelfart, P. A. H.	F.	28	R. 300/125 L. 290/130	R. 135/100 L. 110/90	W.	No
13.	Eppinger, E. C. and Midelfart, P. A. H.	F.	32	R. 140/90 L. 152/120 2. mos. before: R. 116/88 L. 135/90	R. pop. 102/88 L. pop. 100/88 2 mos. before: same as above	W.	No
14.	Evans, W.	M.	23	R. 165/95 L. 155/95	145/–	W.	No
15.	Finesilver, B.	M.	26	R. 230/110 L. 150/110	R. 120/98 L. 105/80	W.	Yes
16.	Flexner, J.	M.	19	R. 238/128 L. 238/128 On subsequent occasions: R. 178/90 L. 178/90	96/72 at time of latter brachial reading, but no pop. readings could be obtained consequently upon repeated attempts.	W.	No

TABLE I—*Continued*

No.	Author	Sex	Age	Blood Pressure		Color	Autopsy
				Arm	Leg		
17.	Follet and Caille, E.	M.	17	R. 210/120 L. 210/120	R. 110/90 L. 115/95	W.	No
18.	Gasser, R. R.	M.	20	3 readings in ½ hr.: 208–190–210 116–118–120	"Hypotension or inability to record pressure in lower extremities."	W.	No
	Subsequent observations by J. T. King	M.	20	R. 160/110 L. 156/120	R. 142/136 L. 140/136. Both pop. barely audible		
19.	Grollman, A. and Ferrigan, J. P., Jr.	M.	25	R. 162/81 L. 176/98	R. 109/80 L. 113/78	W.	Yes
20.	Hamilton, B. E. and Stewart, C. C., Jr.	M.	18	R. 170/84 L. 170/84	95/–	W.	No
21.	Hampson, A. C.	M.	12	R. 145/75 L. 145/75	88/–	W.	No
22.	Hesdorffer, M. B.	M.	18	R. 180/80 L. 190/90	100/80	W.	No
23.	Hodann, C.	M.	44	R. 170/60 L. 165/50	R. 120/–	W.	No
24.	Hunter, D.	M.	14	R. 165/90 L. 155/85	none taken	W.	No
25.	King, J. T., Jr.	M.	35	R. 180/106 L. 180/98	R. 110/– L. 110/–	W.	No
26.	King, J. T., Jr.	M.	58	R. 210/85 L. 160/85 2 wks. later: R. 170/78 L. 155/70	R. 142/80. 2 wks. later: L. 102/90(?)	W.	No
27.	King, J. T., Jr.	F.	40	R. 168–210 80–107 L. 173–230 85–120	R. 140–162 75–110 L. 120–150 72–110	C.	No
28.	King, J. T., Jr. (Courtesy of Drs. Garis and Conley, Union Memorial Hospital)	F.	18	R. 180/106 L. 195/130	No definite determinations could be made in leg	W.	No unpublished
29.	King, J. T., Jr. (Courtesy of Drs. Futcher and Padget, Johns Hopkins Hospital)	M.	15	R. 174/94 L. 142/90	R. 100/70 L. 100/70	W.	No unpublished

TABLE I—*Continued*

No.	Author	Sex	Age	Blood Pressure		Color	Autopsy
				Arm	Leg		
30.	King, J. T., Jr. (Courtesy of Dr. Henry M. Thomas, Jr., Hospital for the Women of Md.)	F.	24	R. 160–210 / 90–110 L. 160–210 / 90–110	110–140 / 70–80	W.	No Unpublished
31.	King, J. T., Jr.	F.	22	R. 180/102 L. 180/102	110/–	W.	No Unpublished
32.	King, J. T., Jr.	F.	33	R. 160/90 L. 160/100	85/80	W.	No
33.	Laffont and Laffargue	F.	42	R. 230/65 L. 230/65	90/60	W.	No
34.	Laubry, C. and Marre, L.	M.	29	R. 215–220 / 90 L. 220/90	155/85–90 L. 150/90	W.	No
35.	Laubry, C., Routier, D. and Van Bogaert, A.	M.	42	R. 200/130 L. 200/130	none in legs	W.	No
36.	Lian, C., Abaza and Frumusan, P.	F.	30	R. 300/90 L. 300/90	140/– lower leg	W.	No
37.	Lichtenberg, H. H. and Gallagher, H. F.	F.	12	R. 210/170 L. 210/170 18 mos. later: 160/90	never obtained in legs	W.	No
38.	Machado, J. de O. and Malheiro, L.	F.	40	R. 350/130 L. 350/130 1 wk. later: R. 195/85 L. 200/85	R. 120/80. L. 120/75 1 wk. later: R. 75/55 L. 75/50	W.	No
39.	Machado, J. de O. and Malheiro, L.	F.	30	R. 190/85 L. 190/90 3 yrs. before: 190/80 (Pachon) both arms	R. 150/90 L. 140/90 3 yrs. before: 130/90 (both)	W.	No
40.	Moncrieff, A.	M.	6	R. 150/100 L. 150/100	—	W.	No
41.	Mussio-Fournier, J.-C. and Barzantini, J.-C.	M.	18	R. 235/90 L. 235/90 3 mos. later: R. 160/65	R. 120/–	W.	No
42.	Pierce, W. F.	M.	35	R. 14/470 L. 14/866	diminished pulsation	W.	Yes

TABLE I—*Continued*

No.	Author	Sex	Age	Blood Pressure		Color	Autopsy
				Arm	Leg		
43.	Pilod and Huguenot	M.	20	R. 165/95 L. 160/90	R. 110/85 L. 100/80	W.	No
44.	Purks, W. K. and Robert, W. P.	M.	14	R. 195/80 L. 180/70	unobtainable	C.	No
45.	Railsback, O. C. and Dock, W.	M.	45	R. 200/100 L. 174/98	R. 164/140 L. 164/130	W.	No
46.	Rösler, H.	M.	35	R. 180/90 L. 185/70	60/–	W.	No
47.	Shapiro, M. J. (This case observed since age 6)	M.	17	R. 178/100 L. 170/100 In later article: 204/100 (R) 185/100 (L)	Unobtainable in either leg	W.	No
48.	Strayhorn, W. D.	F.	26	R. 170/70 L. 170/70	not mensurable	W.	No
49.	Taylor, E. F.	M.	33	R. 162/90 L. 152/98	—	W.	No
50.	Taylor, E. F.	M.	50	R. 260/122 L. 220/160	R. 164/142 L. 134/102	W.	No
51.	Thompson, A. P. and Lamb, F. W.	F.	5	R. 215–175 / 145–120 L. 220–200 / 190–160	125/– popl.	W.	Yes
52.	Ulrich, H. L.	M.	32	R. 210/115 L. 220/115 14 mos. before: R. 194/112 L. 186/108	R. 140/120 L. 140/125 14 mos. before: R. 114/– L. 124/118	W.	No
53.	Ulrich, H. L.	M.	23	R. 140/82 L. 140/78 6 mos. before: 154–144 / 96–86	R. 104/90 L. 104/90 6 mos. before: unobtainable	W.	No
54.	Vega Diaz, F.	—	—	R. 210/110 L. 220/120	R. 145/80 L. 125/95	—	—
55.	Vega Diaz, F., Albert, C. Irigoyen, A. and Suils, E.	M.	13	R. 210/110 L. 220/120	R. thigh 125/80 L. thigh 125/95	W.	No
56.	Wolffe, J. B.	F.	7	R. 206/148 L. 145/100 6 yrs. before: R. 180/40 and 170/50	no pulse felt	W.	No

CASES OF COARCTATION OF THE AORTA FROM 1892 TO 1936, WITH BLOOD PRESSURE READINGS

TABLE II

Blood Pressure 140(S) or More in One Arm

No.	Author	Sex	Age	Blood Pressure		Color	Autopsy
				Arm	Leg		
1.	Arloing, F.	M.	13	190	—	W.	No
2.	Assmann, H.	M.	Young	200/100	120/100	W.	No
3.	Bargi, L.	F.	19	180/60	—	W.	No
4.	Beatty, J. F.	M.	22	R. 160/90	Unobtainable	W.	Yes
5.	Blackford, L. M.	M.	20	R. 150/84	R. fem. 100/–	W.	No
6.	Blumgart, H. L., Lawrence, J. S. and Ernstene, A. C.	M.	47	164/94	88/76	W.	No
7.	Blumgart, H. L., Lawrence, J. S. and Ernstene, A. C.	M.	66	171/96	123/–	W.	No
8.	Bode, O. B. and Knop, F.	M.	40	200/80	—	W.	No
9.	Buday, L.	M.	50	220/70	Not taken	W.	Yes
10.	Davies, G. F. S.	M.	?	180/90	—	W.	No
11.	Dock, W.	M.	45	190/100	Feeble delayed femoral pulse	W.	No
12.	Dock, W.	M.	37	"Hypertension"	Delayed femoral pulse	W.	No
13.	Dock, W.	M.	25	215/85	Feeble delayed femoral pulse	W.	No
14.	Edelman, A. and Maron, R.	M.	25	R. R. 195/45	—	W.	No
15.	Erdmenger, R.	M.	24	140/–(in extremis)	—	W.	No
16.	Evans, W.	F.	45	L. 205/120	R. 85/–	W.	No
17.	Farris, H. A.	M.	11	144/110	Unobtainable	W.	Yes
18.	Farris, H. A.	M.	19	160/90 7 yrs. before: 120/80	106	W.	No
19.	Fray, W. W.	M.	married ?	190/80	—	W.	No
20.	Giroux, M. and Jobin, J. B.	F.	20	220/80	Not taken	W.	Yes
21.	Gossage, A. M.	F.	53	200–225/100	—	W.	No
22.	Graybiel, A., Ashton, A. W., and White, P. D.	F.	29	183/95	100/70 (calf)	W.	No

TABLE II—*Continued*

No.	Author	Sex	Age	Blood Pressure		Color	Autopsy
				Arm	Leg		
23.	Graybiel, A., Ashton, A. W., and White, P. D.	M.	24	162/100	85/65 (calf)	W.	No
24.	Graybiel, A., Ashton, A. W., and White, P. D.	F.	20	163/100	115/65 (calf)	W.	No
25.	Graybiel, A., Ashton, A. W., and White, P. D.	M.	28	177/81	100/65 (calf)	W.	No
26.	Graybiel, A., Ashton, A. W., and White, P. D.	F.	33	160/87	95/60 (calf)	W.	No
27.	Hamilton, W. F. and Abbott, M. E.	M.	14	150/50	—	W.	Yes
28.	Hamilton, B. E., and Stewart, C. C., Jr.	F.	61	R. 160/100	120/– dorsalis pedis. Femoral arteries pulsated faintly. Pop. not made out.	W.	No
29.	Hamilton, B. E., and Stewart, C. C., Jr.	F.	32	180 to 210 / 110	Not more than 100/– above knee	W.	No
30.	Hamilton, B. E., and Stewart, C. C., Jr.	F.	22	R. 150–206 / 90–112	80/– popliteal	C.	No
31.	Hardaway, R. M., and Sawyer, H. P.	M.	38	300+	Not taken	W.	Yes
32.	Hein, G. E.	M.	64	170–180 / –	—	W.	No
33.	Hein, G. E.	M.	55	150/110	—	W.	No
34.	Kövesi, G.	M.	21	170 (Gaertner)	—	W.	No
35.	Kövesi, G.	F.	17	220–230 (Riv. Roc.) 260–265 R. rad. during attack	—	W.	No
36.	Laubry, C., Routier, D., and van Bogaert, A.	M.	19	210/70 (wrist)	110/60 (ankle)	W.	No
37.	Laubry, C., Routier, D., and van Bogaert, A.	F.	24	140/80 (in course of strep. sept.)	None in legs	W.	No
38.	Laubry, C. and van Bogaert, A.	M.	24	1. 230/120 2. 200/120 3. 190/120	130/100	W.	No

TABLE II—*Continued*

No.	Author	Sex	Age	Blood Pressure		Color	Autopsy
				Arm	Leg		
39.	Lemon, W. S.	M.	22	185/80 2 mos. later: 192/72	Could not be recorded	W.	No
40.	Lewis, Sir T.	M.	31	181/123	106 (pop.)	W.	No
41.	Lewis, Sir T.	M.	63	217/102	133 (pop.)	W.	No
42.	Lewis, Sir T.	M.	37	215/107	85 (pop.)	W.	No
43.	Lewis, Sir T.	M.	52	192/97	117 (pop.)	W.	No
44.	Lewis, Sir T.	M.	61	233/103	135/92 (pop.)	W.	No
45.	Lewis, Sir T.	M.	41	202/99	120/– (pop.)	W.	No
46.	Lewis, Sir T.	M.	43	192/89	—	W.	Yes
47.	Lewis, Sir T.	M.	49	213/118	—	W.	Yes
48.	Lian, C., Abaza, and Frumusan, P.	F.	20	180/70–80 at 15 yrs.: 160/70 each arm)	100/60 (oscill.) at 15 yrs.: 100/60, each leg	W.	No
49.	Lian, C., Abaza, and Frumusan, P.	M.	18	160/60 at 15 yrs.: 150/70	110/50 (lower leg) 150/80 (base of thigh) at 15 yrs.: 120/70	W.	No
50.	Lian, C., Abaza, and Frumusan, P.	M.	13	170/90	thigh: 130/60	W.	No
51.	Loeper and Marchal, G.	M.	18	165/100	—	W.	No
52.	Lommel, F.	F.	38	190/–	—	W.	No
53.	Mackenzie, G. M.	M.	5	128/78	—	W.	No
54.	Maxwell, J.	F.	33	270/80	100/–	W.	No
55.	Maxwell, J.	M.	20	200/110	Too low to be accurately recorded	W.	No
56.	Maxwell, J.	F.	34	245/160	Impossible to obtain in either leg	W.	No
57.	Meerseman, F., Bergondi J. and André	M.	21	200/110	100/60	W.	No
58.	Minkowski	M.	23	300/– R. radial	—	W.	No

TABLE II—*Continued*

No.	Author	Sex	Age	Blood Pressure		Color	Autopsy
				Arm	Leg		
59.	Moon, R. O.	M.	17	180/–	Pulsation in fem. was scarcely perceptible	W.	No
60.	Moga, A., and Sireteanu, M.	M.	38	200/120	130–110/–	W.	No
61.	Moga, A., and Sireteanu, M.	M.	35	150/90	120/–(max.) by oscill.	W.	No
62.	Moga, A., and Sireteanu, M.	F.	30	170/– (max.) oscillometer	130/– (max.) oscillometer	W.	No
63.	Parkes-Weber, F.	M.	40	200/85	—	W.	No
64.	Parkes-Weber, F. and Price, F. W.	F.	56	230–290/–	—	W.	No
65.	Parsons-Smith, B. T.	M.	24	144/100	—	W.	No
66.	Pezzi, C., and Agostoni, G.	M.	41	175/125	—	W.	No
67.	Pezzi, C., and Agostoni, G.	M.	69	150/70	—	W.	No
68.	Potain and Bureau	M.	40	220–230/–	—	W.	No
69.	Purks, W. K., and Robert, W. P.	F.	23	150/105	Unobtainable	W.	No
70.	Read, W. T., Jr., and Krumbhaar, E. B.	M.	35	over 200	—	C.	Yes
71.	Rösler, H.	M.	45	180/102	80/–	W.	Yes
72.	Routier, D., and Heim de Balzac, R.	F.	24	140/80	None in legs	W.	No
73.	Santas, M. A.	M.	61	165/–	—	W.	No
74.	Schleckat, O.	M.	44	180/50	—	W.	No
75.	Shapiro, M. J.	M.	6	134/80	Unobtainable	W.	No
76.	Starling, H. J.	M.	40	255/148	—	W.	No
77.	Steiner, R.	M.	20	150–170/–	—	W.	No
78.	Strong, G. F.	M.	18	140/90 (sick with low fever)	—	W.	Yes
79.	Strong, G. F.	M.	38	220/90	—	W.	Yes
80.	Strong, G. F.	F.	12	160/80	—	W.	Yes

TABLE II—*Continued*

No.	Author	Sex	Age	Blood Pressure		Color	Autopsy
				Arm	Leg		
81.	Taylor, E. F.	F.	33	190/60	could not be estimated	W.	No
82.	Taylor, E. F.	M.	21	R. 198/90 Later: 168/82 and 154/64	Not possible to estimate pressure in fem. arteries	W.	No
83.	Taylor, E. F.	F.	59	175/110 A few days later: 180/120	Not taken	W.	No
84.	Van den Berg, Heynsius	F.	29	250+	—	W.	No
85.	Walker, W. G.	M. father	48	R. 158/82	L. 108/94	W.	No
86.	Walker, W. G.	M. son	18	R. 166/108	L. 130/116	W.	No
87.	Werley, G.	M.	35	150/90	Slight oscill. bet. 110 and 100 (thigh) Tycos	W.	No
88.	Wilson, M. G.	F.	20	180–220 / 110–130	120/– (femorals)	C.	No
89.	Woltman, H. W. and Shelden, W. D.	F.	44	150/84	Lower thigh: 100/–	W.	No
90.	Zenoni, C.	M.	66	205–220/–	—	W.	No

these reports to identify the arm from which pressure readings were taken. There are six cases without autopsies in which the pressure was noted from an unspecified arm. If such readings were taken from the left arm, a hypertension in the right might have been overlooked. Lewis [57] points out that heart failure might bring about a fall of previously elevated pressure to within normal limits in some cases. In 15 of the 19 cases in this group there seems to have been either circulatory embarrassment, or gross failure, or chronic sepsis, sufficient to have reduced a previously elevated blood pressure to normal. Blackford's [9] patient (case 3) complained of respiratory distress, including orthopnea, but developed neither cyanosis nor edema. The patient reported by Canciulescu and Missirliu [14] (case 5) was a boy of 14 years, who had had a protracted illness and who came under observation with signs of serious infection, cyanosis and circulatory insufficiency.

Hein [41] seems to have reported a case of coarctation in which the circulation was compensated and in which a normal arm pressure was found. His patient complained of some dyspnea and cardiac pain but the circulation

CASES OF COARCTATION OF THE AORTA FROM 1892 TO 1936, WITH BLOOD PRESSURE READINGS

TABLE III

Blood Pressure of Arms Less than 140 (S)

No.	Author	Sex	Age	Blood Pressure		Color	Autopsy
				Arm	Leg		
1.	Anderson, R. G., quoted by Parkes-Weber and Knop	M.	44	112/60	—	W.	Yes
2.	Bahn, K.	M.	40	115/75	—	W.	No
3.	Blackford, L. M.	M.	24	R. 128/88 L. 122/90	—	W.	No
4.	Bode, O. B. and Knop, F.	M.	54	120/70	—	W.	Yes
5.	Canciulescu, M. and Missirliu, V.	M.	14	115/85	85?	W.	No
6.	Focken, E.	F.	18	R. 115/– L. 105/–	—	W.	No
7.	Fray, W. W.	M.	57	122/86	—	W.	Yes
8.	Hein, G. E.	M.	32	122/80	—	W.	No
9.	Hein, G. E.	M.	60	120/85	—	W.	No
10.	Hinrichsmeyer, C.	M.	32	130–110 95–85	—	W.	No
11.	King, J. T., Jr.	F.	25	R. 138/90 L. 120–125/80	90/80	W.	No unpublished
12.	Kurtz, C. M., Sprague, H. B. and White, P. D.	F.	14	90/65	—	W.	Yes
13.	Kuschelewski, B. P., Glikin, M. I. and Sysslin, D. M.	M.	40	115–105 60–50	Not taken	W.	Yes
14.	Parkes-Weber, F. and Knop, F.	M.	54	125/70	—	W.	No
15.	Pereiras, R., Inclan, R. and Perez de los Reyes, R.	M.	7	105/–	—	W.	Yes
16.	Smith, F. M. and Hansmann, G.	M.	17	120/60	—	W.	Yes
17.	Stewart, H. L. and Bellet, S.	M.	26	R. 126–136 60	Not taken	W.	Yes
18.	Strassner, H.	M.	36	130/– R. Rad.	—	W.	Yes
19.	Umber	M.	22	R. 101/97 L. 95/92	—	W.	No

seems to have been fairly adequate. Unfortunately in this case (number 8) no note was recorded as to which arm was used for the pressure determination.

CASES OF COARCTATION OF THE AORTA FROM 1892 TO 1936, WITH BLOOD PRESSURE READINGS

TABLE IV

Mixed Blood Pressure Readings: High in One Arm and Low in the Other

No.	Author	Sex	Age	Blood Pressure		Color	Autopsy
				Arm	Leg		
1.	Amberg, S.	M.	16	172/– and 108/–	100 and 94 (thigh)	W.	No
2.	Amberg, S.	M.	13	170/– and 90/–	Could not be recorded by usual means	W.	No
3.	Blackford, L. M.	F.	44	R. 164/86 L. 126/110	R. femoral 90/80	W.	No
4.	Deneke, T.	M.	46	R. 185–220 / 85–90 L. 106–120(?)	—	W.	No
5.	East, T.	M.	55	R. 135/100 L. 195/145	140/105	W.	No
6.	Hesdorffer, M. B.	M.	23	R. 178–210 / 90–110 L. 108–120 / 92–90	—	W.	No
7.	Ratschow, M. and Arendt, J.	?	?	R. 155/75 L. 95/60	90/85	W.	No
8.	Turkington, S. I.	M.	23	R. 210/10 L. 130/80	110/–	W.	No
9.	Villafañe, A. P. and Menendez, E. B.	M.	20	R. 215/115 L. 115/–	—	W.	No
10.	Woltman, H. W. and Shelden, W. D.	M.	20	R. 164/86 L. 126/110	A few slight oscillations bet. 80 and 90	W.	No

Hence, there is no well defined case so far recorded in which the circulatory compensation was above suspicion and in which the pressure in both arms was found to be normal.

UNREPORTED CASES

Case 1. A young white woman of 18 years was seen at the Union Memorial Hospital through the kindness of Drs. Garis and Conley. She was admitted at the hospital for a lower right quadrant pain.

Past history was essentially negative, though some mild attacks of palpitation following exercise had been experienced over the previous six months. *The physical examination* showed a rather marked exaggeration of all pulsations in the upper extremities, especially that of the innominate. There was also a well marked pulsation in the second right interspace at the sternum, thought to be due to the mammary artery. Pulsations were felt in both interscapular regions near the scapulae at the level of the spines. A pulsating vessel of the size of one's finger was felt on each side. On the left, it was about three inches in length. On the right, while definite, it was less marked. There was a rough systolic murmur in both interscapular regions,

being loudest near the first dorsal spine. *Heart:* The P. M. I. was exaggerated. Presystolic gallop was heard and a soft apical systolic murmur. Cardiac dullness was a trifle full to the left, measuring 9.5 cm. to the left of the midline, 4 cm. to the right. *Pulse* was bounding and of good volume at the wrists, but the abdominal aorta gave no appreciable pulsation. No pulse was felt over the femoral, dorsalis pedis or posterior tibial arteries. *The blood pressure* in the left arm was 195 systolic and 130 diastolic and in the right 180 systolic and 106 diastolic. No definite determination could be made in the legs and oscillations of the blood pressure needle were almost negligible. *The electrocardiogram:* Rate 110. Rhythm regular. Conduction intervals: P–R 0.18 second. Left axis deviation. T-waves upright in Lead I, biphasic in II, inverted in III. The laboratory findings were as follows:

Urine: Sp. gr. 1.018. Appearance yellow and cloudy. Acid reaction. No albumin or sugar. There were no red cells, white cells or casts, but a large number of epithelial cells were seen.

The red cell count was 4,620,000, hemoglobin 102 per cent (Sahli). The white cell count was 13,500 with 81 per cent P. M. N. and 19 per cent lymphocytes. The stained smear showed normal red cells and platelets. One c.c. of phenolphthalein intravenously yielded 70 per cent the first hour and 5 per cent the second hour. Non-protein nitrogen was 29 mg. per 100 c.c., and fasting blood sugar 140 mg. per 100 c.c.

Teleroentgenogram showed erosion of the inferior margin of the posterior part of most of the ribs, with slight cardiac enlargement to the left.

Case 2. A white woman, married, aged 24, was seen at the Hospital for the Women of Maryland through the kindness of Dr. Henry M. Thomas, Jr., who had made the diagnosis of coarctation of the aorta. The patient was a primipara, admitted to the obstetrical department in May 1934 when about four months pregnant. The family history was entirely unimportant. The past history revealed that the patient had been short of breath since childhood and had noticed an occasional sense of fluttering and some pain in the precordial area. She was not permitted to take part in athletics or gymnastic work at school by a physician's order. She was first examined in 1929 and was told that she had hypertension. Examination at the time she was three months pregnant showed blood pressure 200 systolic and 100 diastolic. The urine was clear. One month before delivery, non-protein nitrogen of the blood was 24 mg. per cent. In November 1934, the patient entered the hospital and after the first stage of labor, lasting 11 hours, was delivered readily by low forceps (Scanzoni maneuver). The baby, a normal male, was in good condition. The puerperium was non-febrile and uncomplicated. The post partum examination showed blood pressure 160–210 systolic, 90–110 diastolic in the arm; in the legs it was 110–140 systolic, 70–80 diastolic. Dr. Thomas discovered bilateral pulsations in the back just medial to the vertebral borders of both scapulae. There was the usual systolic murmur best heard in the interscapular region.

Laboratory tests were as follows:

Urine examinations were consistently negative for sugar and albumin.

Mosenthal test showed concentration power of 0.007.

Phthalein test showed an appearance time of 5 minutes with half hour excretion of 50, 15, 10 and 5 per cents for a two hour total of 80 per cent.

Blood Wassermann was negative.

Blood chemistry on 6/19/34: non-protein nitrogen 26 mg. per cent. Uric acid 2.4 mg. per cent. Creatinine 1.3 mg. per cent. A repetition showed on 10/16/34: non-protein nitrogen 24 mg. per cent; uric acid 2.6 mg. per cent; Co_2 combining power 61 volumes per cent. *Teleroentgenogram:* Notching of the inferior rib margins. Cardiac shadow within normal limits. Defect in region of aortic knuckle in both antero-posterior and oblique views.

Remarks: This patient was carefully observed during pregnancy, but was thought

to be suffering from malignant hypertension. While she was delivered without complications, she was advised to avoid further pregnancies.

Case 3. A white, single woman of 22. She was a patient at the Johns Hopkins Hospital in July 1932, complaining of high blood pressure, kidney trouble and burning on urination. Family history contained nothing of relevance. The patient had been subject to frequent headaches with dizziness. She had nocturia two or three times. The urine was quite normal. The gynecological examination was normal. The physical examination was as follows:

There was a distinct difference in the degree of pulsation in the arms as compared with the legs. The abdominal aorta was barely felt and pulsation in the femorals and dorsalis pedis was not made out. There was no history of nocturia prior to one year ago, no intermittent claudication, but she had suffered from numbness and coldness of legs requiring her to get out of bed and use or rub the legs. On careful palpation very slight left dorsalis pedis pulsation was felt. There was mottled cyanosis of the lower legs. P. M. I. was vigorous when patient was supine. There were no shocks or thrills. Dullness was about 4 by 7½ cm. No increased retromanubrial dullness. Sounds vigorous at apex with soft systolic blow, practically absent in erect posture. Accentuation of A_2 and P_2. Systolic murmur of moderate intensity heard over root of the aorta, no diastolic; very large pulsation in episternal notch. Bilateral pulsating vessels about the size of small finger just at the inner margin of each scapula running roughly up and down. No appreciable murmur on the right side; short rough systolic murmur in left interscapular region, at about the level of the spine. Arteries of fundi very tortuous and there was definite slight pulsation of the arterial trunks. Vessels were more numerous than normal.

Teleroentgenogram: Typical rib erosions. "Chimney" shaped aortic shadow. No cardiac enlargement.

Further examination revealed chronic tonsillitis and enlarged adenoids. Basal metabolic rate was between + 15 and + 23 per cent, without definite signs of hyperthyroidism. *Blood pressure:* arms 180 systolic and 102 diastolic; legs 110 systolic, and diastolic not known.

The electrocardiogram was normal. T_3 was inverted. Blood chemistry nonprotein nitrogen 31 mg. per cent. Phenolsulphonephthalein elimination was 65 per cent for 2 hours. Urinary concentration test showed a variation of specific gravity from 1.002 to 1.026. Only 130 c.c. of urine were passed between 7 p.m. and 7 a.m. as against 1825 during the preceding day. Blood Wassermann reaction negative. *Diagnosis:* Isthmus stenosis.

Case 4. A 15 year old white boy, seen by courtesy of Dr. T. B. Futcher. There was no complaint. Family history was negative. Past history: tonsillectomy at two years of age. Present illness: Patient has no symptoms under ordinary circumstances. Specifically, there is no dyspnea on ordinary exertion. When running, he is conscious of shortness of breath but there is no palpitation or precordial distress. There is no edema and no nocturia.

The physical examination was negative except as noted below: the retinal arteries were distinctly tortuous but showed no A–V compression and there were no hemorrhages or exudates. There was no cardiac shock or thrill. Pulsation of dorsal scapular arteries was well felt in both interscapular areas. The radial pulses were full, bounding—the right apparently of higher tension and fuller volume than the left. No pulsation was felt in the abdominal aorta, femoral or popliteal arteries. Pulsation could barely be felt in the posterior tibial and dorsalis pedis arteries. The blood pressure in the right arm was 174 systolic and 94 diastolic; in the left arm 142 systolic and 90 diastolic; in both legs about 100 systolic and 70 diastolic. Pulse was regular, not accelerated. At the apex was heard a soft systolic murmur which disappeared on exercise. Over the base a harsh systolic murmur was heard which was trans-

mitted upward and outward on both sides. It was heard best in the two interscapular areas.

The Wassermann reaction was negative. Blood non-protein nitrogen 43 mg. per cent. Red blood cells 5,020,000; hemoglobin 15.4 gm.; white blood cells 5,500. Phenolsulphonephthalein kidney function test showed 75 per cent elimination in 2 hours. The urine was normal.

It is of some interest that the erosion of the under surfaces of the ribs is already apparent in the roentgenogram of this patient. The cardiovascular stripe is also of

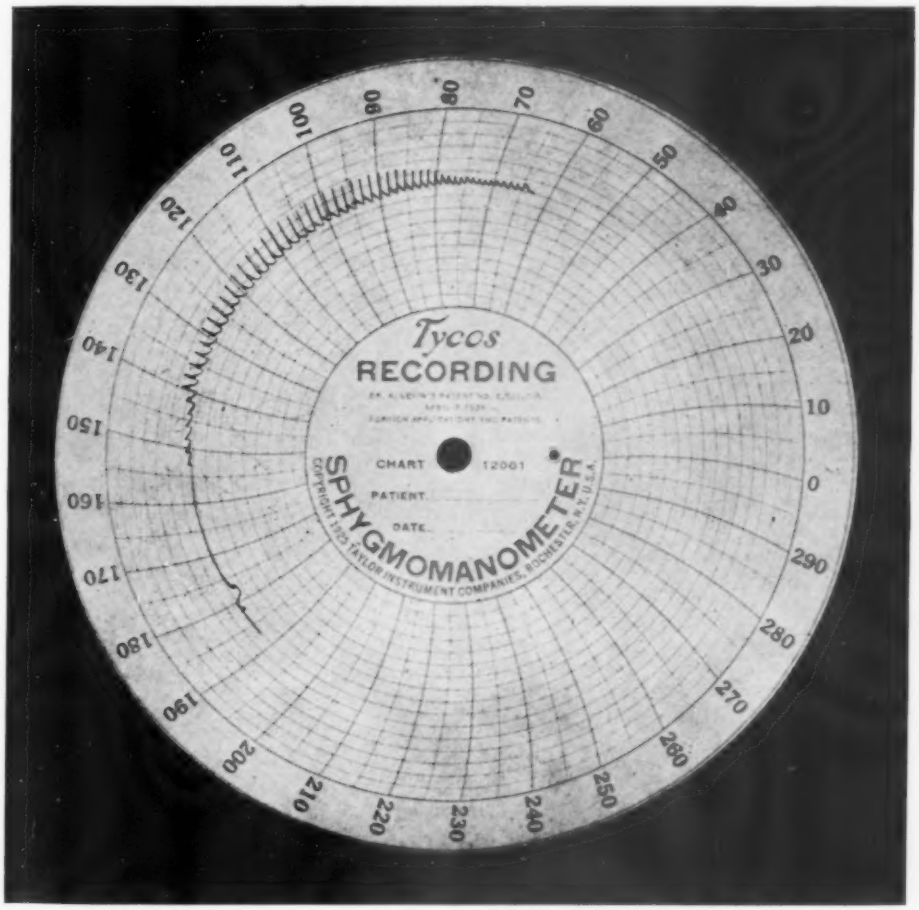

FIG. 1. Record of blood pressure from right arm in case 5. Systolic level is about 138; diastolic, about 80.

typical contour. Unfortunately, there are no previous roentgenograms to indicate the age at which rib erosions became apparent. The heart was not enlarged.

Case 5. A white matron, aged 25, of Jewish extraction, consulted me in January 1929. The family history was not relevant. She had had one healthy child, no miscarriages. A second healthy child was born in 1930. There was no complication with either pregnancy.

The single persistent symptom was excruciating headache, which had tormented the patient as far back as she could remember. My impression on seeing her in 1929

was that the headaches were probably associated with the isthmus stenosis of the aorta, possibly due to actual aneurysm of the cerebral vessels. However, there was no severe headache from the time of her second pregnancy until I saw her in 1932.

The immediate symptom for which this patient consulted me was cardiac palpitation, of extrasystolic type.

The examination follows: The patient looks well but somewhat lean. Color good. Very slight increase in pulsations in the neck. Axillaries are visible but not the ulnar vessels. *Eyes:* Pupillary reactions normal. Transient lid-lag. *Nose:* Nor-

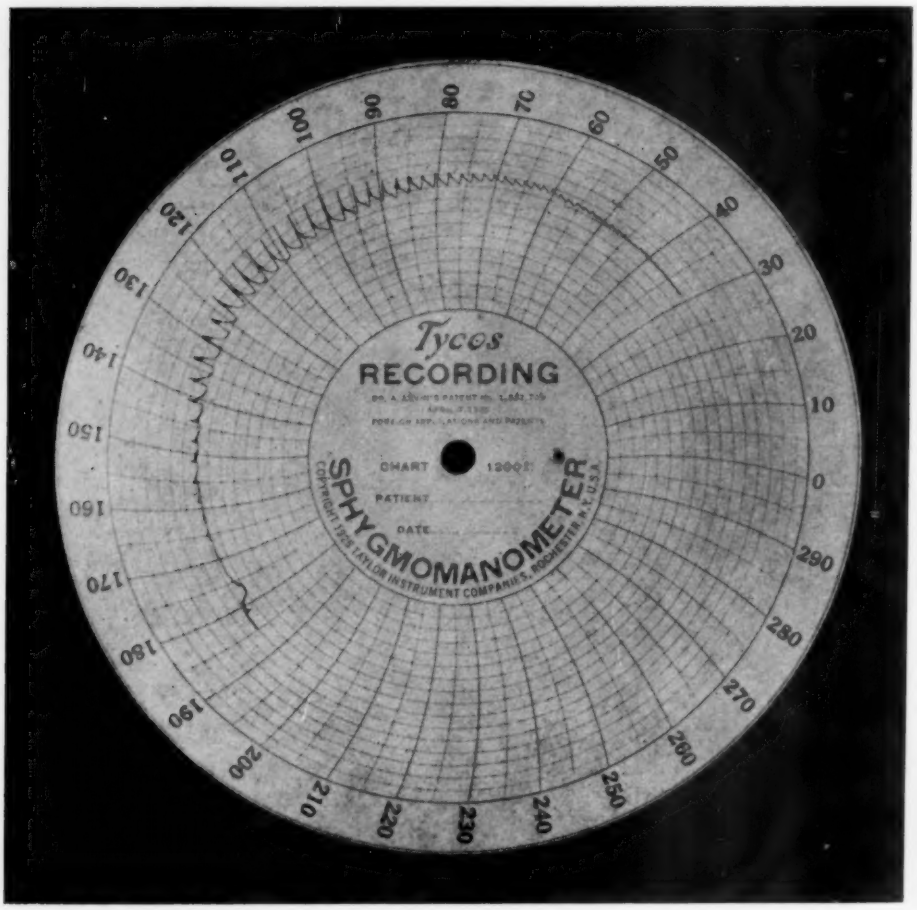

FIG. 2. Blood pressure from left arm in case 5. Pressure about 123/87.

mal. *Mouth and throat:* Quite normal. Tonsils small. *Glands:* Cervicals not enlarged. *Thyroid:* Normal. *Chest:* Resonant. Breath sounds normal. No retromanubrial pulsation and no significant dullness. *Back:* There is a definite pulsation along the inner margin of the left scapula, but I find it difficult to outline the shape of the vessel. A similar vessel is felt in the right interscapular region. They feel like the usual collateral vessels in such cases but are smaller. There are no other collateral arteries to be felt over the back. There is a moderately intense systolic murmur in each interscapular region. A systolic murmur is heard over the entire

back of the chest to within 3 fingers-breadth of the right base and all the way to the left base. It is a little louder in the left interscapular region than anywhere else. Breath sounds everywhere normal. No râles.

Heart: P. M. I. is made out in the fourth space, in the natural position. No shock or thrill. Rather marked pulsation in the region of the pulmonary conus. Cardiac dullness: right 3.5 cm., left 8.5 cm. Sounds at apex perfectly normal. There is a barely audible systolic blow. At the base both second sounds are slightly increased. There is a grating systolic murmur over the pulmonic area referred to the left clavicle.

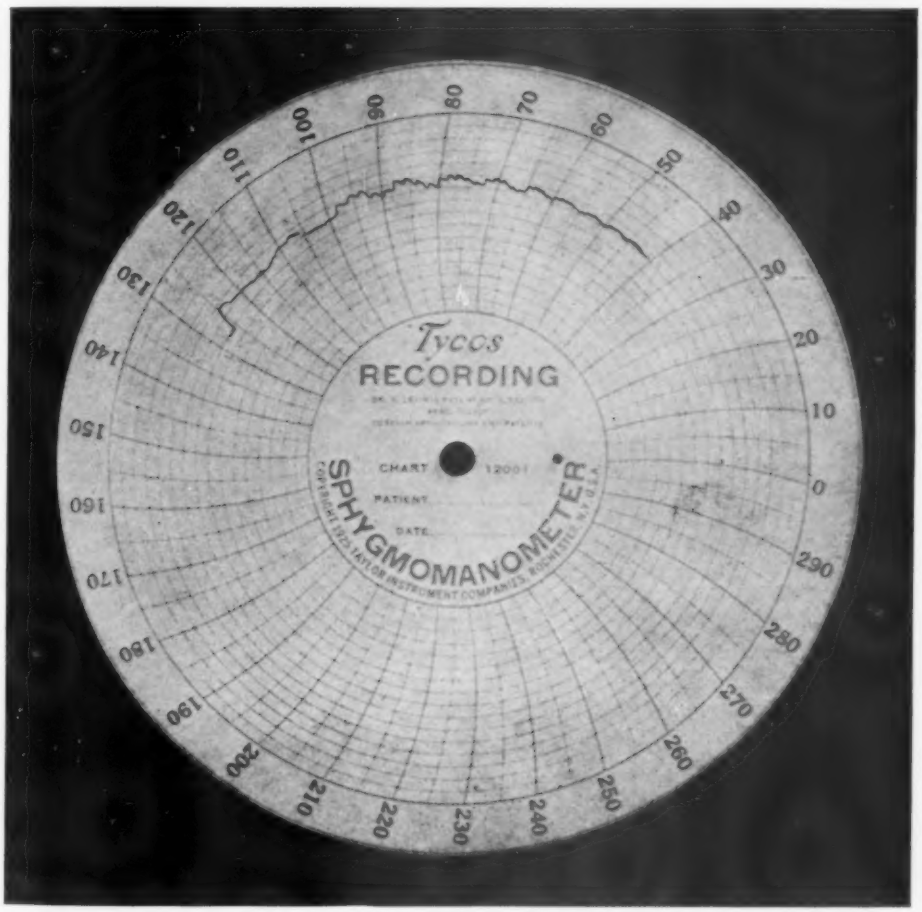

FIG. 3. Showing extreme reduction of pulsation in leg, with systolic blood pressure less than 100. Case 5.

Abdomen: On deep palpation a slight but definite pulsation is made out in the abdominal aorta. There is also a slight pulse to be felt in the right femoral artery but this is much reduced from normal. A similar pulsation on the left. Cecum is palpable. Liver not made out, neither is the spleen.

I can feel no pulsation in the left dorsalis pedis, nor in the right. There is a very slight pulse in the right posterior tibial and in the left.

Pulse: At the wrist is big, regular. Rate 84.

Blood pressure: Right arm: 122 systolic and 66 diastolic at 2:30 p.m. (two hours after lunch which included tea. Smoked a few cigarettes after lunch). Left arm: 128 systolic and 66 diastolic.

Blood pressure 1/30/29: Right arm 122 systolic and 60 diastolic. Left arm 120 systolic and 60 diastolic.

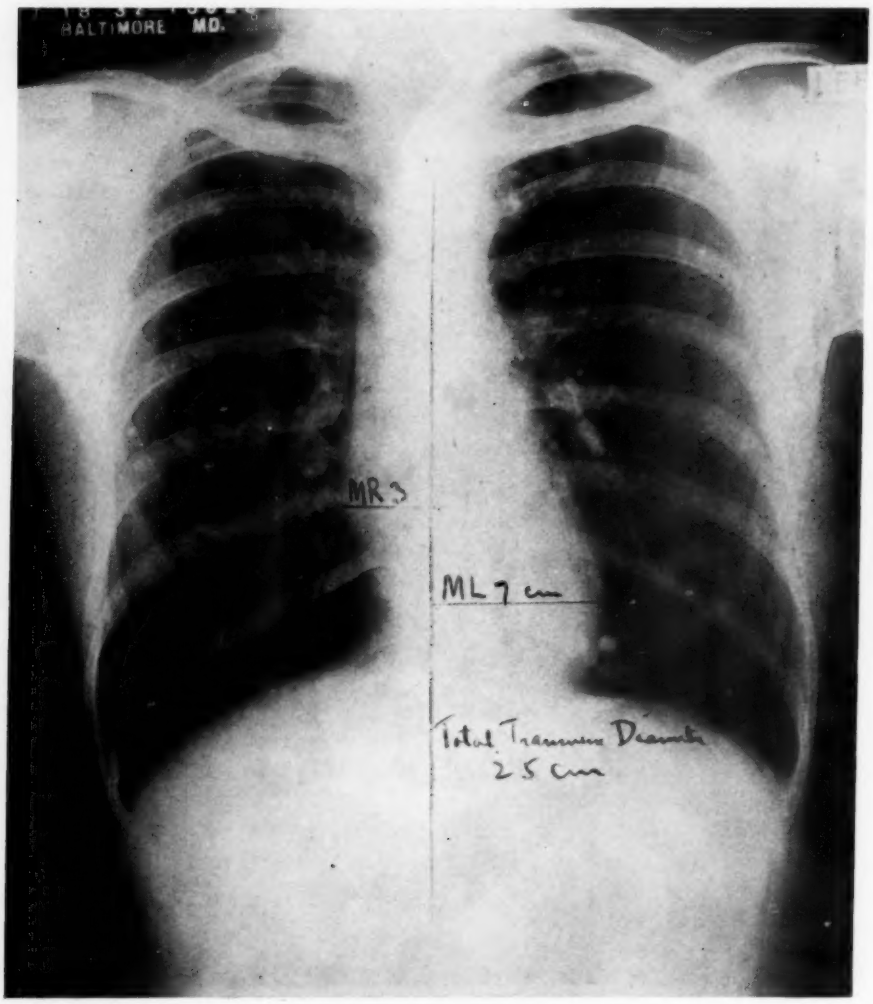

FIG. 4. Film from case 5, showing characteristic tubular aortic shadow. Somewhat deficient at the knuckle without rib erosion.

Right popliteal 104 systolic and 90 diastolic. Left popliteal 108 systolic and 90 diastolic. (See figures 1, 2, 3.)

Electrocardiogram: Rate 100. Rhythm regular. P-waves upright and slightly notched in Leads I and II, especially in II, diphasic in III. R-waves of normal sequence. P–R 0.15 sec. Q–R–S 0.06 sec. S–T normal. T-waves upright, normal. Diagnosis: normal tracing.

Dr. C. A. Waters' Roentgen-Ray Report: "The roentgen-ray examination of the chest fails to show any erosion of the under surfaces of the ribs due to pressure from hypertrophy of the intercostal arteries. The ascending arch of the aorta looks to be a little enlarged and there is also some prominence of the innominate artery. The descending arch is not at all prominent and the heart is unusually small; the transverse diameter measuring only 10 cm. divided as follows: M. R. 3 cm., M. L. 7 cm. The transverse diameter of the chest is 25 cm. There are numerous calcified glands noted, chiefly on the left side. There is no parenchymal infiltration. The apices are essentially clear. There is certainly nothing in the roentgen-ray examination to indicate coarctation of the aorta." (See figure 4.)

Diagnosis: 1. Isthmus stenosis (coarctation) of the aorta.
2. Extrasystolic arrhythmia.

Comment. The recordings of the blood pressure showed a systolic level in the right arm of about 138, with a diastolic level about 80; in the left arm the recorded pressure was 123 systolic and 87 diastolic. In the leg, the oscillations were minute and occurred between 90 and 100 mm. There was definite evidence of collateral arterial circulation in the interscapular region and a well marked systolic murmur, maximum in the left interscapular region. These findings seem to establish the diagnosis of isthmus stenosis beyond reasonable doubt; however, the relative normality of the arm pressure and the lack of rib erosions suggest that the degree of narrowing is not great. This is the only case of coarctation I have seen in which the arm pressure was within normal limits.

Discussion and Conclusions

It is clear from the tables that hypertension in the arms is the rule in cases of coarctation of the aorta. The pressure in the right arm is usually higher than that in the left and there is a group of nine cases in which this difference was so marked that the systolic pressure in the left arm was within normal limits. At the same time, it is not unusual to find a diastolic hypertension in the left arm in the face of a normal systolic level.

Mention should be made here of the numerous observations of asymmetric blood pressure in the two arms that have been noted in apparently normal individuals. For example, Korns and Guinand,[48] taking 10 mm. Hg as the upper limit of normal discrepancy, found asymmetry of the brachial pressure in 22 per cent of apparently normal subjects. In this group with discrepancy in the two arms, the higher pressure existed in the right arm in three-fourths of the cases. Stieglitz and Propst [93] have recorded similar findings. In their cases 15.7 per cent showed asymmetric brachial pressure readings, the higher pressure in the majority of cases being found in the right arm. Various postulates, such as cervical rib, aortitis, arteriolar spasm, injury, arterio-venous aneurysm and central trophic disorders are suggested as possible causes of such discrepancy.

However, the second report shows that asymmetric readings of pressure are most to be expected at the extremes of pressure, either high or low, and that the discrepancy tends to disappear as the pressures approach normal. This observation, together with the high incidence of asymmetry reported by Korns and Guinand [48] in supposedly normal persons, suggests that such differences in the two arms are probably common among normal subjects,

especially when the pressure is determined only once. Doubtless, some of the discrepancies can be attributed to organic bases, such as cervical rib.

These findings tend to minimize the significance of such differences in brachial pressure as are recorded in table 1. It is true, however, that the inequality is rather more constant and striking among the cases of coarctation than might be expected in cases of generalized hypertension, though there can be no certainty of this until a large number of observations on the brachial pressures of hypertensive subjects becomes available. At any rate, it becomes clear that many of the discrepancies of pressure in table 1 are probably within normal limits.

Table 4 is more difficult to explain on the basis of normal variation. Korns and Guinand [48] reported a maximal difference of 38 mm. Hg and an average of 14.3 mm. in their group with asymmetric pressures. It is possible, even likely, that an organic basis existed to explain some of these discrepancies. The differences of pressure in table 4 are beyond the maximal systolic difference noted by Korns and Guinand [48] in all but one case, and in that case it was exactly 38 mm.

For these reasons, the presence of hypertension cannot be relied upon as a certain index to isthmus stenosis. If the pressure is taken in the left arm, a normal pressure might be found even in the presence of a marked hypertension in the right arm. Cases that have progressed to a state of cardiac failure or cases in which there has been a chronic infection or other debilitating disorder, may show a pressure in both arms that has fallen from an abnormally high level to within normal limits.

Case 5 in the present series also indicates that erosion of the ribs is not necessarily present in a typical coarctation. It is known that rib erosions may not be present in childhood, but in case 5 the patient was an adult. It is my belief that the demonstration of collateral arterial circulation is the most important single clue to the diagnosis of coarctation. It has been present in each of some 16 cases I have seen. Moreover, the incorporation of a search for collateral arterial pulsation in the interscapular region into a routine physical examination is readily achieved. The finding of typical murmurs in the back is also in my opinion a more important single clue than the level of blood pressure in the arm.

Finally, mention should be made of the fact that Lewis [57] emphasized the regularity with which hypertension could be expected in the adult variety of coarctation, provided the slighter degrees of narrowing were excepted together with those cases in which cardiac failure or protracted illness might have lowered a previously elevated pressure to within normal limits. In case 5 of this present series there is reason to believe that the degree of stenosis is not great, though a typical collateral circulation was found, together with a striking difference in the degree of pulsation and in the pressures of arms and legs. We have no way of determining whether the stenosis in this case is of the infant or adult type. The fact remains, how-

ever, that coarctation sufficient to produce characteristic physical signs and asymmetry of pressure between arms and legs may exist in an adult together with normal arm blood pressure.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

MASSIVE ATELECTATIC COLLAPSE OF THE LUNG COMPLICATING PNEUMOCOCCUS PNEUMONIA *

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MASSIVE atelectatic collapse of one or more lobes of the lung, occurring during the course of primary lobar pneumonia or complicating recovery from this disease, has been recognized by very few writers. In most articles dealing with pneumonia, either this complication is not mentioned at all or it is merely dismissed as a possible but exceedingly rare complication. Several reports of its occurrence in the pneumonias of infants and children have appeared during the past few years [1-10] but very few instances have been recorded in cases of acute lobar pneumonia in adults,[11-31] although it was recognized as far back as 1881, or even earlier.[11]

The characteristic findings of massive atelectasis involving one lobe or one lung have been recognized in the roentgenograms in 62 cases of primary pneumococcus lobar pneumonia in adults at the Boston City Hospital in the past seven years. During the same period, varying degrees of atelectasis were noted in the lungs at necropsy in 47 cases of pneumococcus pneumonia of various kinds. A number of the cases exhibited striking clinical features. It is of interest, therefore, to present briefly some illustrative cases and to review separately some of the features of the cases recognized by roentgen-ray and of those noted at autopsy.

CASES REPORTED IN THE LITERATURE

The early history of pulmonary atelectasis in relation to pneumonia is recorded in the studies of Rommelaere.[11] According to this writer, Laennec encountered this condition in pneumonia with effusion, and Grisolle and Traube used the words " splenisation " and " carnification " which they considered to represent different types of inflammation. Rommelaere described most of the physical signs and anatomical findings in atelectasis occurring during pneumonia and emphasized the presence of mucoid sputum and the lack of displacement of the cardiac impulse in differentiating this condition from pleural fluid. He also noted that bronchophony and bronchial breathing may be present in some cases while in others the breath sounds may be entirely absent. He believed that the collapse occurred only outside the

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inflamed portion of the lung and that the sudden appearance of this collapse may be the cause of death in some cases. He described two such cases; one was diagnosed by the failure to obtain fluid by thoracentesis and the second, which occurred during an otherwise uneventful convalescence three weeks after the onset of typical lobar pneumonia, was diagnosed by physical signs and confirmed at autopsy.

Recent interest in massive collapse of the lung dates from two important groups of observations made by Wm. Pasteur, the first relating to collapse of the lower lobes occurring in cases of diphtheria and ascribed to paralysis of the diaphragm [32] and the other to a similar condition occurring after abdominal operations and considered by him to be due to reflex inhibition of diaphragmatic movement.[33] The condition has since been frequently recognized and described as a complication in a variety of conditions including: (1) surgical operations, (2) trauma to the chest or elsewhere, (3) after hemoptysis in pulmonary tuberculosis, (4) in cases of bronchiectasis, (5) obstruction of bronchi due to foreign bodies or tumors, or (6) from pressure outside the bronchus, and (7) in nervous and debilitated individuals with pulmonary hypoventilation. An extensive bibliography is included in a recent paper by Bowen.[34] Inasmuch as the primary interest in the present paper concerns atelectasis as a complication of pneumonia, only the literature pertaining directly to this subject will be cited.

As previously noted, massive atelectasis indicated by a shift of the mediastinal contents to the affected side, has been encountered more often in the pneumonias of infants and children. Thoenes [1] reported 11 cases in which this condition was definitely demonstrated in the roentgenograms. Most of his children were undernourished and had atypical pneumonias, but cases of typical unilateral lobar pneumonia in previously healthy children were also included. One or more lobes of the right lung were affected in 10 of his 11 cases, the upper lobe being most frequently involved. There were autopsies in four of these cases. In two the heart had returned to a normal position, in one there was partial atelectasis and in the fourth massive collapse with the mediastinum pulled over to the affected side. Wallgren [2] reported eight cases in children ranging in age from six months to nine years. The involvement was right-sided in three and left-sided in five, and probably began during acute pneumonia. Some of his cases may have had the atelectasis at the time of the onset of the pneumonia. All had cleared after intervals varying from a few weeks to a year. Griffith [3] criticized the observations of the last two authors mainly on technical grounds. However, in careful roentgen studies in 40 cases of pneumonia in young children, he noted definite and sometimes marked displacement of the heart to the affected side with subsequent return to normal position in 16 cases with unilateral involvement, but did not make sufficient observations to determine when this condition began or how long it lasted. Although admitting that atelectatic patches in the consolidated lung might aid the displacement, this writer ascribed the condition to overdistention of the unaffected lung. Tal-

lerman and Jupe [4] described a similar occurrence in five children, including three with lobar pneumonia and two with bronchopneumonia, in all of whom the condition cleared completely. In one of their cases there was pneumonia with atelectasis on the right side which cleared at the time when the left lung became involved with pneumonia but without atelectasis. They considered the cardiac displacement due to both the partial collapse of the affected lung and the push of the sound overdistended lung. Findlay [5] reported the case of a child of seven who, when first seen one, possibly two weeks after the onset of a pneumonia, was afebrile but had much mucopurulent sputum. Partial collapse of the left lower lobe was noted by physical and roentgen examination. He noted bronchial breathing and increased spoken voice at some examinations and absent breath sounds at others. The condition cleared completely in 2½ weeks after a roentgen-ray examination with lipiodal, followed by carbon dioxide inhalations. Gleich [6] reported a case of lobar pneumonia of the right lung in a child with complete situs transversus in whom the physical signs alternated between those of atelectasis and those of consolidation for six weeks. Ellis [7] reported eight cases of atelectatic bronchiectasis in children. In five of his cases there was a typical history of pneumonia in which the symptoms persisted for an unusually long time and bronchiectasis with atelectasis was present when they were first seen five or more years later. A sixth case had a typical right lower lobe pneumonia with fever for 16 days. On the thirty-third day collapse of the right lower lobe was diagnosed by roentgen-ray on the basis of a dense triangular shadow in the cardio-hepatic angle. This cleared up completely with breathing exercises in two months, and no bronchiectasis developed. Nordgren [8] reported the case of a girl of 14 years, with a long asthmatic history, in whom massive atelectasis with induration and scoliosis developed in the right lower lobe one month after the onset of typical lobar pneumonia in this lobe, and in whom the lungs were entirely clear one month later. He ascribed the atelectasis to occlusion of bronchi with pneumonic exudate. Anspach [9] studied 50 cases presenting, by roentgen-ray, a triangular shadow at the base of the lung in the cardio-hepatic angle, both with and without bronchiectasis. Some of these cases had bronchopneumonia without foreign bodies in the bronchi at autopsy. Some later developed bronchiectasis, while others cleared without developing bronchiectasis. The commonest history was that of an acute pulmonary process with physical signs of lobar pneumonia followed by decreased breath sounds. In 41 cases there was pneumonia with collapse. He ascribed the collapse to obstruction by pneumonic exudate, the bronchiectasis developing if the atelectasis persists. Blanton and Morgan [10] reported the sudden onset of massive atelectasis of the right lung in a five weeks old infant on the ninth day after the onset of a pneumonia of the right lower lobe and three days after the fever had subsided. This infant had paroxysms of cough followed by vomiting, the vomitus containing sticky

mucus. Within a week there was patchy aeration of the lung and the heart returned to normal position after one month.

Fewer instances of this complication have been noted in the pneumonias of adults. Gwynn [12] reported two cases in elderly patients with typical lobar pneumonia of the right lower lobe, who had a sudden episode of extreme dyspnea lasting several hours, after which massive collapse of the right lung with the heart markedly displaced to that side was demonstrated clinically. In the first patient the collapse occurred on the nineteenth day of illness during an otherwise uncomplicated convalescence with resolution, and in the second it occurred on the fourth day of an acute illness during which there was much mucoid sputum. A third patient, who had bronchitis or bronchopneumonia of the left lower lobe, also had a similar episode with collapse of the entire left lung. In each of these cases, the heart returned to normal position in five to seven days. Peppard [13] reported four cases in which collapse occurred in the right lung 10, 8, 6, and 2 days, respectively, after the onset of pneumonia, the lungs previously being noted as having pneumonia without collapse. In three of these cases there was typical lobar pneumonia and the left side was later involved without evidence of atelectasis. The fourth patient was described as having bronchopneumonia and the collapse cleared in three days, whereas in the other three cases it cleared more slowly. Jacobaeus [14] reported a case of lobar pneumonia of the right upper lobe in which collapse suddenly occurred on the eighteenth day and gradually cleared within six months. The location of the lesion and the delay in clearing suggested pulmonary tuberculosis but this was ruled out by repeated negative sputum examination and by the subsequent course. A second patient had central pneumonia and developed collapse of the right lower lobe. Jacobaeus [15] also reported a case of acute bronchitis with scattered râles, but more on the left side. On the third day of illness this patient had an attack of dyspnea which was found to be associated with massive collapse of the left lung and a shift of the mediastinal contents to that side. The condition had cleared completely three weeks later. Mohler [16] reported two cases. The first had marked dyspnea following a vomiting spell, and collapse of the right lung was demonstrated six hours later. The patient had slight fever but no leukocytosis and cleared rapidly and completely. The second case had typical pneumonia of the right upper and middle lobes and auricular fibrillation. The pneumonia was apparently clearing on the sixth day but the patient was raising thick tenacious sputum. On the ninth day there was evidence of collapse of these lobes by physical examination and in the roentgenogram. Corrylos and Birnbaum [17, 18, 19] presented extensive experimental evidence and some clinical data to support their contention that lobar pneumonia is merely a lobar atelectasis with infection. They advocated bronchoscopic aspirations, while Henderson [20] advocated carbon dioxide inhalations for treatment early in the disease. Mainzer [21] reported two cases in which typical collapse of the lung was

rapidly relieved by bronchoscopic aspiration of gelatinous material. The condition was ushered in with chill and fever, in each case. Wu [22] and Graeser, Wu and Robertson [23] reported a careful study of the roentgenographic findings and physical signs in 40 cases of lobar pneumonia in adults. Elevated diaphragm on the affected side was noted in 18 cases. In four cases they observed a definite shift of the mediastinal contents to the affected side during resolution. This was especially marked in one case in which it lasted at least 29 days but the lungs had returned to normal in two months. There were three other cases with slight but definite atelectasis during the acute disease, and they have observed another more striking case outside the series in which the collapse was noted on the second day of illness. Two of the cases died three to four days after the last observation, and the mediastinal contents were found at autopsy to be in normal position. Hart [24] noted that displacement of the heart, trachea, and diaphragm to the affected side is common in pneumonia. Korol [25] suggested roentgenograms in suitable positions to differentiate empyema from large areas of atelectasis in cases with prolonged signs and symptoms. Rigler [26] presented the roentgenograms of a rare case, in which the entire right lung was dense but the mediastinum was in normal position on the fifth day, but in which after an acute attack of dyspnea and cyanosis 12 hours later, the heart and trachea were shown to be definitely displaced to the right, indicating a superimposed atelectasis. Sante [27] also mentions this complication as a rare occurrence during resolution with rapid absorption of pneumonic exudate without removal of the material obstructing the bronchi. Davidson and Freedman [28] reported a case of atelectasis and fibrosis of the left lower lobe which presumably began as a collapse complicating pneumonia 25 years previously, when the pulmonary symptoms began. Fletcher and Dimson [29] reported a case of pneumonia of the left lower lobe in which atelectasis was first demonstrated on the eleventh and again on the twenty-first day after the onset of pneumonia, but was shown to have cleared entirely four months later. Mayoral [30] included among his cases of "shrunken lung" two in which the condition was attributable to lobar pneumonia. One had an earlier history of pneumonia and presented atelectasis of the right lower lobe with the heart displaced to that side. Biopsy of the partly occluded bronchus showed only fibrosis. The other case had a prolonged convalescence from pneumonia of the right lung without atelectasis demonstrable in the first roentgenogram. A second roentgenogram 20 days later and a third, six weeks after that, showed fibrosis and unresolved pneumonia with atelectasis and the heart was displaced to the right. Butler [31] reported a case of post-pneumonic empyema associated with atelectasis in which there was poor healing and failure of the cavity to close although there was no air in the pleural cavity. In the roentgenogram the underlying lung looked dense, suggesting carcinoma. Bronchoscopy showed stenosis of the major bronchus without foreign body, tumor, or exudate. Rapid improvement

followed this procedure and later no collapse could be demonstrated in the bronchus.

Cases from the Boston City Hospital

Many cases of pneumonia have been encountered in which repeated examinations revealed physical signs over the affected lobes alternating between those suggestive of fluid and those indicative of frank consolidation. This has occurred during the acute illness or at various stages during an otherwise uneventful convalescence. In a number of such cases, evidence indicating varying degrees of atelectatic collapse of the lung may be obtained by carefully noting the position of the heart, trachea, and diaphragm at each of the examinations. The signs of atelectasis can not always be verified by the roentgenogram unless it is ascertained that the characteristic signs are present immediately before and after the film is taken and necessary precautions in technic are observed to avoid distortion and to maintain comparable perspective in successive films. When massive atelectasis involves an entire lobe—either one that was previously uninvolved, or a partially consolidated lobe, or one in which resolution has already progressed to the point where a good proportion of the exudate has been removed or absorbed from the alveoli—the physical and roentgen-ray signs are easy to discern provided that this condition is borne in mind.

In the present study, two groups of cases will be considered. The first group includes cases in which the clinical and roentgenographic evidence of frank lobar pneumonia was unmistakable and specific types of pneumococci [35] were obtained from the sputum or blood, or both. Cases following operations, parturition, and injuries were excluded. Inasmuch as the physical signs and even roentgen-ray findings of minor degrees of atelectasis in acutely ill patients are not always convincing unless special precautions and technics are employed,[23, 36] only those cases in which obvious massive collapse of one or more lobes was observed in the roentgenograms were selected. Sixty-two cases observed between 1929 and 1936 are included in this group. Certain features of these cases are analyzed in table 1. The second group comprises 47 cases of pneumococcus pneumonia (both lobar and atypical) in which atelectasis of various degrees was made out at autopsy. In each instance, type-specific pneumococci were cultured from the consolidated lung and other sources at autopsy and, in almost every instance, the same type pneumococcus was obtained during life. Although one or more roentgenograms were made in most of these cases, atelectasis was not definitely diagnosed from these films. These two groups of cases will be considered briefly and abstracts of a few cases selected to illustrate certain clinical features will be presented. A considerable number of cases not included in these two groups exhibited roentgen-ray evidence of moderate to marked elevation of the diaphragm on the affected side without shift of the mediastinal contents. Since it is reasonable to assume that this con-

dition may result solely from reflex inhibition of diaphragmatic movement, these cases have been omitted although some may indeed represent cases of massive collapse.

Cases Showing Massive Atelectasis in Roentgenograms (*Table 1*). The collapse was first made out during the acute disease in 34 of the 62

TABLE I

Analysis of 62 Cases of Pneumococcus Lobar Pneumonia in Which Massive Atelectatic Collapse of the Lung Was Recognized in Roentgenograms

A. Collapse First Seen during the Acute Disease				*B.* Collapse First Seen during Resolution				
Day of First X-Ray Showing Collapse	Number of Cases	Previous X-Rays Without Collapse	Later X-Rays Without Collapse	Day of First X-Ray Showing Collapse	Number of Cases	Previous X-Rays Without Collapse	Later X-Rays Without Collapse	No Previous X-Rays Taken
1	2	–	–	7	1	0	1	1
2	3	–	2	8	3	0	3	3
3	5	–	3	10	4	3	1	1
4	2	–	1	11	4	4	2	0
5	6	–	2	12	1	0	0	1
6	5	1	1	14	3	3	1	0
7	4	1	3	15	3	3	2	0
8	3	1	1	16–21	4	3	2	1
9	4	–	2	22+	5	5	1	0
Total	34	3	15	Total	28	21	13	7

C. Lobes Involved		*D.* Age Groups		*E.* Pneumococcus Types			
Lobes	Cases	Years	Cases	Type	Cases	Type	Cases
Right lower	20	12–19	1	I	23*	XI	1
Right upper	9	20–29	6	II	7†	XIII	1
Right lower and middle	6	30–39	21	III	3	XIV	1
Right lung	20	40–49	20	IV	2	XVII	1
Left lower	5	50–59	11	V	5	XVIII	1
Left lung	2	60–69	1	VII	5‡	XIX	1
		70+	2	VIII	9	Neg. I–XX	2

* Including 9 serum treated.
† Including 2 serum treated.
‡ Including 2 serum treated.

cases. In three of these cases, previous films showed pneumonia without evidence of collapse; in the remaining cases the collapse was noted in the first film. Later films showed the return of the mediastinal contents to normal position in 15 of these cases. In most of the other cases no later

films were taken because of the favorable and apparently uncomplicated convalescence or because death ensued. One case showing atelectasis on the first day still showed the mediastinal contents deviated to the affected right side 12 days later.

Six of these 34 patients died, and autopsies done in four failed to show atelectasis. In one of these autopsied cases there was organizing pneumonia in the right lung. This lung had been shown by roentgen-ray to be collapsed 24 days before death, but not 16 days later. In the other three autopsied cases, death occurred on the fifth, eighth and ninth day of illness or four, five, and four days, respectively, after the atelectasis was demonstrated by roentgen-ray. Of the two patients who died and had no autopsy, one had a second roentgenogram showing the mediastinum in normal position and in the other the atelectasis was demonstrated on the day of death.

Fluid was demonstrated by thoracentesis in four of the surviving cases at the time when the mediastinum was deviated to the affected side. In two instances this fluid was sterile and resorbed spontaneously, and in the other two it was infected and required treatment by open thoracotomy and rib resection.

There were 28 cases in which the collapse was first made out in roentgenograms taken after the fever and acute symptoms of pneumonia had subsided. In 21 of these cases, previous roentgen-ray films showed the characteristic findings of lobar pneumonia but no evidence of mediastinal displacement. In the remaining seven cases no previous roentgen observations were available. Subsequent roentgen-ray films showed that the mediastinal contents had returned to their normal position in 13 cases before the patient left the hospital. In most of the remaining cases either the collapse was still present or no further observations were available during the patient's stay in the hospital. Observations were made in four patients for three to 27 months after they left the hospital. In all of these four patients, the mediastinal contents were displaced to the affected side at the time of discharge from the hospital but, in three of these cases, they had returned to normal position at the time of the last observation. The day of the disease when collapse was first noted, the lobes involved, the age of the patients, and the pneumococcus types in these cases are summarized in table 1.

*Cases of Pneumonia with Atelectasis at Autopsy.** Some of the more relevant features of these cases are analyzed in table 2. The 47 cases of this group occurred among 684 cases of pneumococcus pneumonia in which autopsies were done at the Mallory Institute of Pathology of the Boston City Hospital during the seven years ending July 1936.[37] As in the first group, cases occurring after operations, parturition, and injuries were omitted. No definite evidence of collapse was noted during life in any of these cases except in the two cases of bronchogenic carcinoma. It is ap-

*We are indebted to Dr. Frederick Parker, Jr., for permission to use the autopsy protocols.

TABLE II

Certain Features of 47 Cases of Pneumococcus Pneumonia in Which Pulmonary Atelectasis Was Found at Autopsy

	Number of Cases
A. Probably congenital atelectasis	1
(*a*) Infant, aged 4 days; bronchopneumonia, Type XI	
B. Atelectasis probably due to obstruction	4
(*a*) Carcinoma of bronchus; 2 cases of bronchopneumonia (Types I and VI)	
(*b*) Inhaled food and bronchopneumonia, 2 cases:	
(1) Infant, aged 2 days, Type XIX	
(2) Perforated esophagus, age 30 years, Type VI	
C. Atelectasis associated with compression from pleural fluid	13
(*a*) *Types:* I, 5; V, 2; III, IV, XI, XII, XIII and XVIII, 1 each	
(*b*) *Ages:* Newborn, 1; 12 to 29 yrs., 3; 40 to 49 yrs., 3; 50 to 59 yrs., 3; 60 to 69 yrs., 2; 70+ years, 1	
D. Partial or scattered atelectatic collapse	13
(*a*) Bronchopneumonia, 4; Lobar pneumonia, 9	
(*b*) Resolution and organization in collapsed lobe, 6	
(*c*) Hypostatic (?)—involving postero-inferior portions, 4	
(*d*) Early pneumonia in the collapsed lobe—?extension, 2	
(*e*) Atelectasis only in consolidated lobes, 6; only in non-consolidated lung, 5; in consolidated and non-consolidated lobes, 2	
(*f*) *Types:* I, 1; II, 2; III, 1; IV, 2; V, 2; XII, 2; VIII, IX, XVIII, 1 each	
(*g*) *Ages:* 2 mos., 1; 2 yrs., 1; 40 to 49 yrs., 4; 50 to 59 yrs., 5; 60 to 69 yrs., 1; 70+ yrs., 1	
(*h*) *Duration of illness:* 10 days, 4; 11 to 15 days, 2; 20+ days, 5; unknown, 2	
E. Massive atelectatic collapse	16
(*a*) Bronchopneumonia, 4; Lobar pneumonia, 12	
(*b*) Resolution and organization, 8	
(*c*) Collapse involving consolidated lobe only, 4; Collapse of non-consolidated lobe only, 11; Collapse of consolidated and uninvolved lung, 1	
(*d*) *Lobes collapsed:* Rt. upper, 1; Rt. middle, 2; Rt. lower, 4; Rt. upper and middle, 2; Rt. middle and lower, 3; Left lower, 3; Left lung, 1	
(*e*) *Types:* I, 5; II, 2; III, 2; V, 4; VI, 1; VII, 1; XIV, 1	
(*f*) *Ages:* 5 mos., 1; 30 to 49 yrs., 3; 50 to 59 yrs., 4; 60 to 69 yrs., 2; 70+ yrs., 6	
(*g*) *Duration of illness:* 9 days or less, 9; 10 to 21 days, 4; 30+ days, 3	

parent from the table that several varieties of atelectasis are represented among the cases of both lobar and atypical pneumonia.

There was an impressive number of cases in which large portions of the lung were collapsed. In many instances the collapsed portions showed only slight congestion without inflammatory changes while in others there was evidence of resolution and organization with a comparatively small amount of residual exudate. It is not unlikely that acute collapse of such extent may have been the chief cause of death or a major contributing factor in the outcome in some of these patients who had already been suffering from reduced aeration due to the inflammatory consolidation in other lobes.

Abstracts of Cases. It is of interest to mention briefly a few cases selected to illustrate special features of atelectasis complicating pneumonia.

Case 1. Sudden and violent onset of massive atelectasis during the stage of resolution. T. K., a 48 year old man, whose previous history was non-contributory except for a mild illness suggesting "pleurisy" early in 1928, was admitted to the hospital January 18, 1929. On January 1 he had coryza and a dry cough. This lasted one week and was followed by mild diarrhea, malaise, anorexia, and headache lasting

another week. On January 15 he had a severe chill followed by sharp pain in the left chest and cough productive of tenacious bloody and later rusty sputum, all of which continued to the time of admission. The physical findings were those of lobar pneumonia of the left lower lobe. Sputum and blood culture yielded Type I pneumococci. Felton's Type I concentrated antibody was given intravenously in small divided doses during the first four days (total of 45 c.c.). Although the consolidation had spread to involve the entire left lung, there was a gradual subsidence of fever and discomfort. Daily blood cultures after serum therapy remained sterile. The physical signs of resolution were present throughout the left lung on January 24, but the patient remained markedly prostrated. During the night of January 31, the patient was suddenly awakened with intense dyspnea and restlessness, and the pain in the left chest which had previously subsided, recurred with increased severity. These symptoms subsided within a half hour after an injection of morphine. A few hours after this episode the characteristic physical signs of massive collapse of the left lung were present. The breath sounds in the left infraclavicular region were amphoric in character. There was copious mucopurulent sputum. Evidence of resolution returned but the displacement of the trachea and heart to the left side persisted during the patient's stay in the hospital. They were less marked at the time of discharge on March 13, 1929. This patient's course was further complicated by a phlebitis of the left femoral vein accompanied by a low-grade fever beginning February 5 and lasting for two weeks. Numerous sputum examinations during and after the acute illness failed to show tubercle bacilli. The patient was examined one year later, at which time no abnormal signs were made out in the chest. The patient had been symptomless during the intervening 15 months.

A roentgenogram taken on January 19 showed mottled cloudiness of the lower two-thirds of the left chest with the heart and trachea in normal position. Seven films taken at intervals after the attack of acute dyspnea showed the trachea and heart markedly displaced to the left, but those taken before discharge showed definite clearing especially in the lower lobe. A film taken in June 1930 showed the trachea and heart in normal position and the lung fields normal.

Case 2. Latent onset of massive collapse during a severe infection—delayed resolution, and fibrosis of collapsed lung. M. W., a 52 year old man, entered the hospital November 12, 1930, with the typical history and physical findings of a severe lobar pneumonia of six days' duration and involving the entire right lung. An upper respiratory tract infection was present for one week prior to the onset. Type I pneumococci were obtained from sputum and blood culture. Large amounts of concentrated antipneumococcus serum were given between November 14 and 20. Repeated blood cultures were positive until November 16 but later ones were sterile. The jaundice, cyanosis, distention, and physical signs of consolidation present on admission continued until November 25. Staphylococcus abscesses and decubitus ulcers developed over the thighs during this time. Thereafter, there was gradual improvement but marked prostration and weakness persisted. On November 21 the physical signs of atelectasis were made out and the trachea and heart were markedly displaced to the right. These signs persisted until the time of discharge, February 10, but much moisture appeared in the affected lung and the lower lobe showed marked clearing. Bronchoscopy was done by Dr. L. M. Freedman on two occasions, during which much mucopurulent material was removed and attempts were made to inflate the lungs, but the collapse remained. The sputum was repeatedly searched for tubercle bacilli but none were found. The patient returned to the hospital six weeks later and another series of four bronchoscopic aspirations and lipiodal injections was done over a period of several weeks. The lower lobe cleared completely but the upper lobe remained contracted and showed definite evidence of fibrosis. The lipiodal failed to enter the bronchi of the upper lobe.

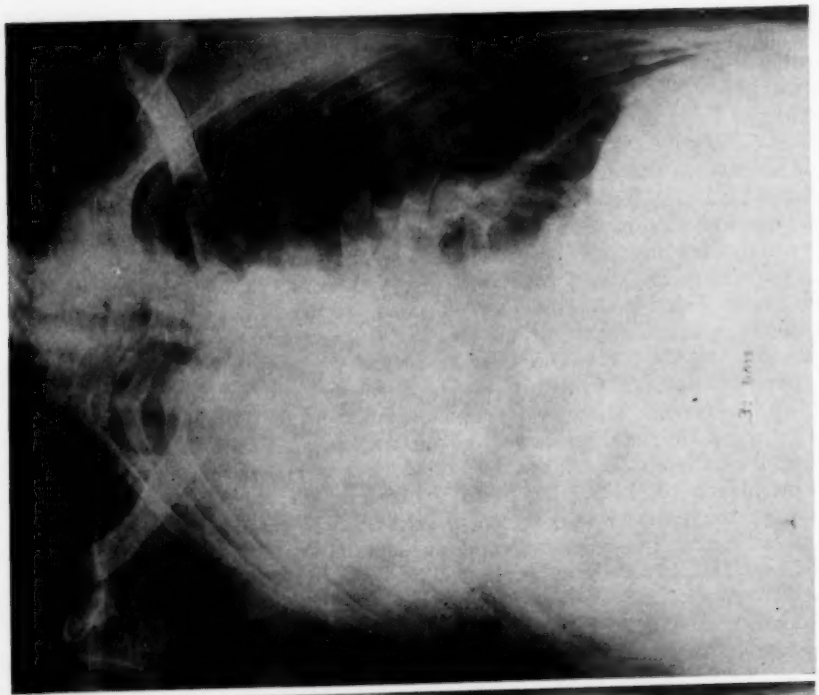

Fig. 1.

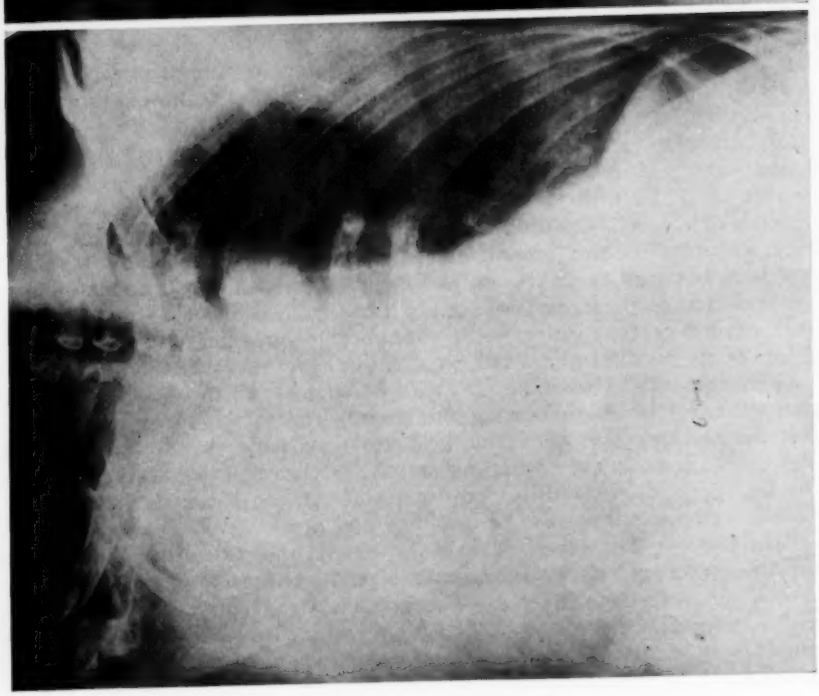

Fig. 2.

FIGS. 1 and 2. Roentgenograms in case 2 showing massive pneumonia of the right lung on the sixth day, and retraction of heart and trachea and clearing lower lobe on the thirty-first day.

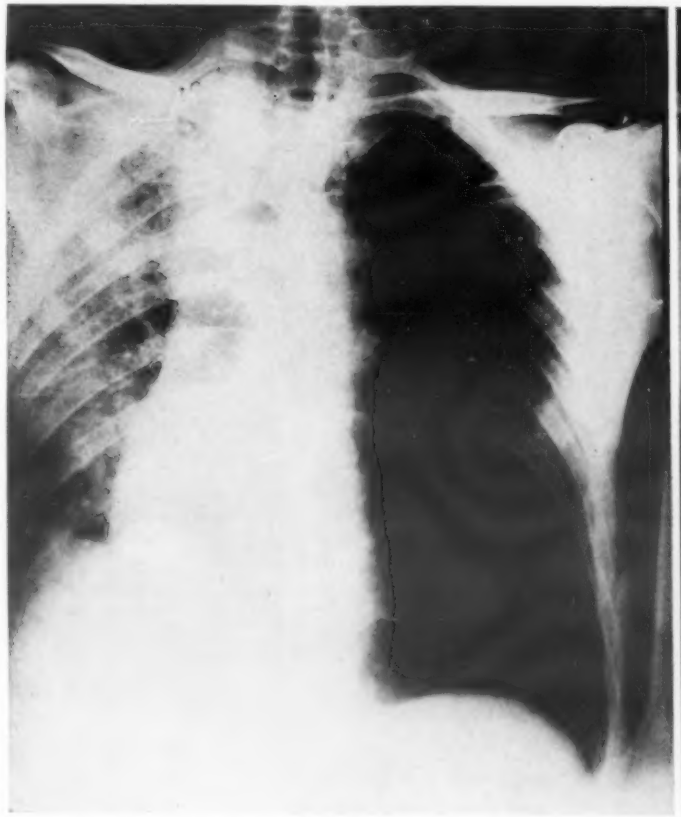

Fig. 3.

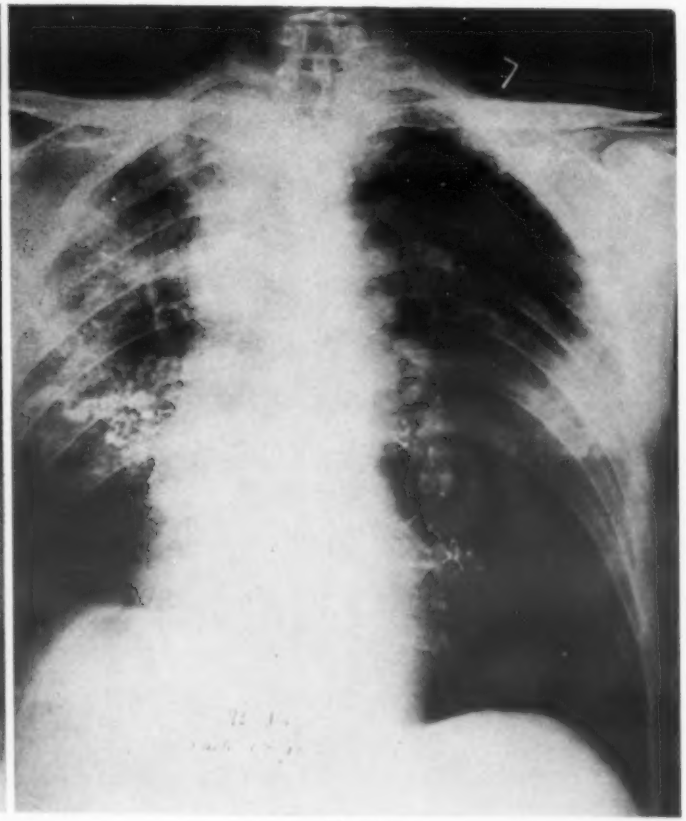

Fig. 4.

FIGS. 3 and 4. Roentgenograms taken one and two months respectively after the film in figure 2. Note the high right diaphragm with the heart and trachea on the right in figure 3. There is partial restoration of the heart with evidence of fibrosis in the right upper lung in figure 4 (taken after the sixth broncho scopy and lipiodal injection).

The first roentgen-ray taken on the day of the earlier admission showed a dense right lung with the heart and trachea in normal position. The next plate taken four days later and numerous roentgen-ray plates taken during the subsequent four months showed the mediastinal contents still displaced to the left, but the later films showed that the lower and middle lobes had cleared and the bronchi to these lobes were outlined by the lipiodal which failed to enter the bronchi of the upper lobe (figures 1 to 4).

Case 3. Latent onset of massive collapse in a patient with pneumonia of moderate severity. C. J., a 38 year old male, entered the hospital February 11, 1931, with typical lobar pneumonia of four days' duration involving the right lower lobe. He had had a cold and slight cough for four weeks previously. The sputum showed pneumococci which failed to agglutinate with the available antipneumococcus serums, Types I to XX, inclusive, and repeated blood cultures showed no growth. The patient had a mild illness with crisis February 18 after which time the physical signs of resolution alternated with those of fluid in the left lower lobe. During the first week in April the lung cleared almost completely. There was a moderate amount of mucopurulent sputum. Roentgenograms taken on February 12, 15, 18, and 24 and on March 2 all showed pneumonia of the right lower lobe. In the two latter plates the density was quite marked suggesting the presence of fluid. Films taken on March 8, 15, 19 and 30 all showed a markedly elevated right diaphragm, the heart displaced to the right, and the rib spaces on the right contracted but the trachea was not much displaced. A film taken on June 15 showed definite but incomplete clearing of the lung and the heart restored to normal position (figures 5 to 8).

Case 4. Pneumonia complicated by atelectasis and empyema. M. N., a 34 year old woman with a negative respiratory history except for influenza in 1918, entered the hospital May 20, 1930, at the end of the fourth day of a severe lobar pneumonia involving the entire right lung. Type I pneumococci were found in the sputum and blood culture. The patient received large amounts of specific antipneumococcus serum for four days during which the initial toxemia and dyspnea gradually subsided but sweating, prostration, marked leukocytosis, and the physical signs of fluid appeared and persisted. Later examinations showed the trachea to be markedly displaced to the right and loud amphoric breathing was heard in the right infraclavicular region. The subsequent appearance of coarse moist râles in this area suggested the presence of pulmonary tuberculosis with cavitation. Numerous examinations of the sputum for tubercle bacilli were negative. A roentgenogram taken May 21 showed a dense right lung but the trachea and heart were not displaced. A subsequent plate taken on May 27 and several later ones showed marked atelectasis of the right upper lobe with retraction of the trachea to that side. Signs of resolution appeared in the upper lobe which remained collapsed throughout the 12 weeks' stay in the hospital. She had rib resection and drainage, and the wound healed completely. The patient returned after 18 months at which time no physical or roentgenologic signs of collapse could be demonstrated and the lungs were entirely clear.

Comment

No attempt has been made to estimate the frequency with which atelectasis complicates the course of pneumonia. The careful studies of Griffith [3] and of Graeser, Wu and Robertson [23] in small groups of cases would indicate that this complication is not infrequent. The cases reported in this paper by no means represent all of the cases of pneumonia in which the condition has occurred in this hospital, but have been selected only because of the definite involvement shown in the roentgenograms or because the condition was noted at autopsy. Minor degrees of atelectasis probably occur at various

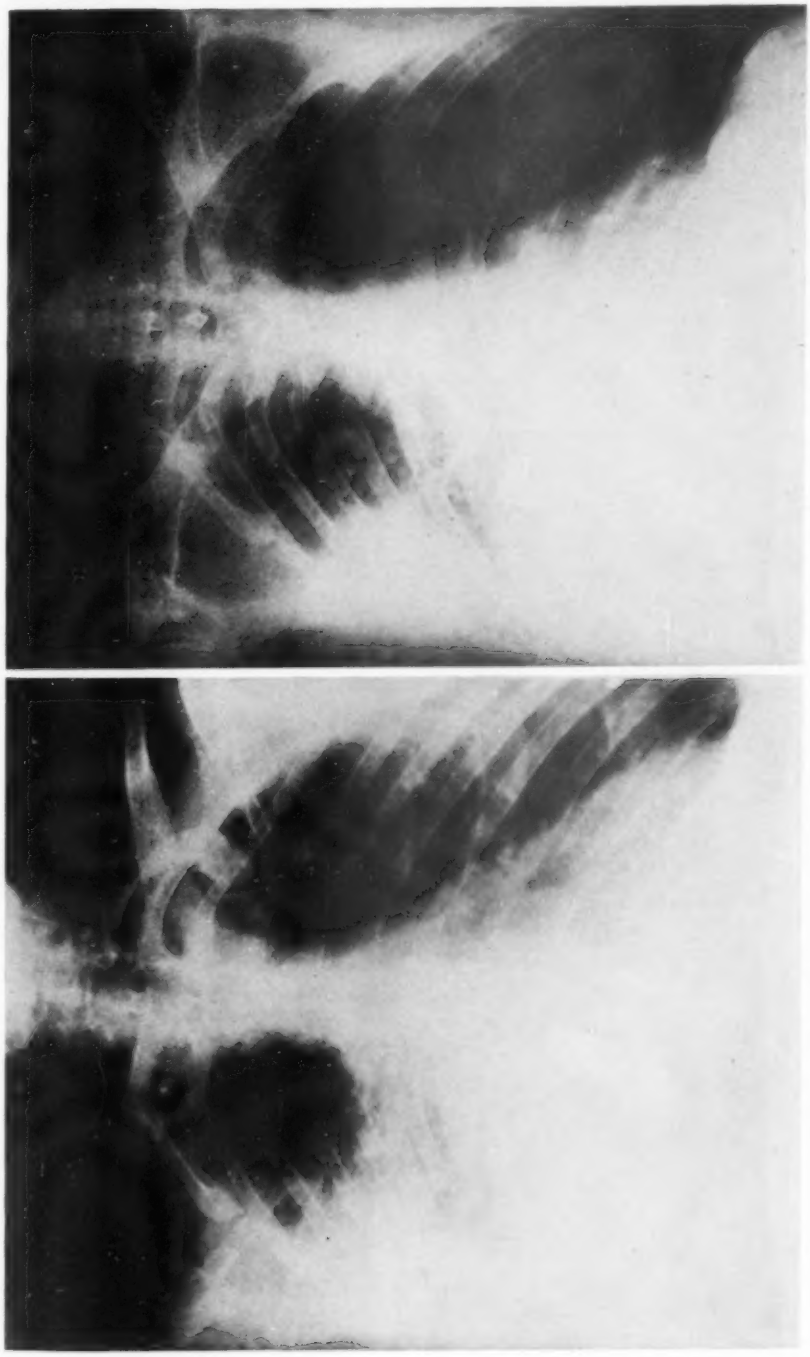

Fig. 5.

Fig. 6.

FIGS. 5 and 6. Roentgenograms taken on the fourth and twenty-third day, in case 3. Note the heart and trachea displaced to the affected side in the second film.

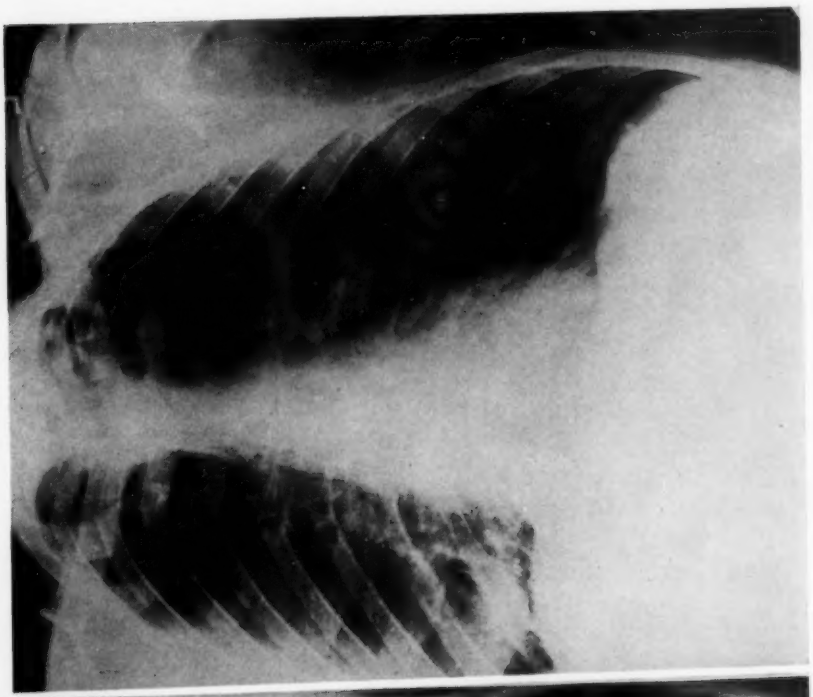

Fig. 8.

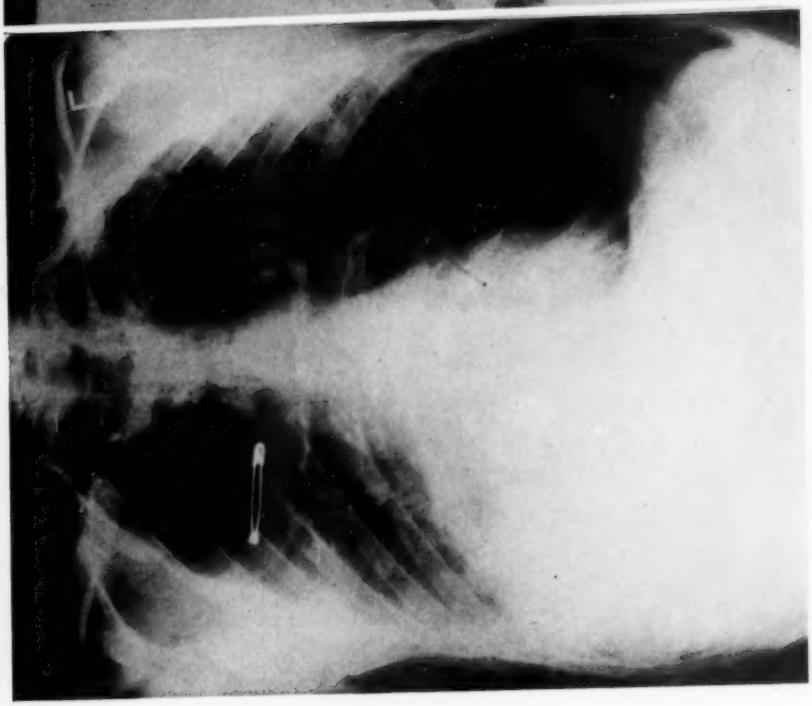

Fig. 7.

FIGS. 7 and 8. Roentgenograms taken one and four months respectively after the one shown in figure 6. Note the high diaphragm and shift of heart and trachea to the right in figure 7 and almost complete clearing in figure 8.

stages in most cases of pneumonia but they probably are of no significance because they are usually temporary and not extensive.

The pathogenesis of this condition can be reasonably explained in the light of the present knowledge of the various mechanisms which may bring about collapse of the lung under a variety of conditions. Contraction of the partly consolidated lung early in the disease or of the partly resolved lung later is aided by the occlusion of bronchi with the unexpelled thick exudate, by the reflex inhibition of diaphragmatic movement due to the fibrinous pleuritis and is probably aided by the push of the overdistended normal lung from the opposite side. The shallow breathing during the acute illness which is common during the active disease and which is continued during the subsequent period of prostration is another factor pointed out by Goldite [38] and others. In other words, most of the various mechanisms suggested by previous writers may be operative in different individuals or in the same case.

Another possibility suggests itself, namely that previous damage to the lung has resulted in a loss of the normal resiliency and thus predisposes to atelectasis when pneumonia occurs. In the present cases 44 per cent of the patients with collapse gave a previous history of pneumonia, and a history of probable previous pulmonary infection was present in a considerable proportion of the cases reported in the literature, even among those in infants and children. In 1000 consecutive cases of pneumococcus pneumonia in this hospital, a previous history was elicited in only 16.5 per cent [39] and a similar frequency of previous pneumonias has been noted by others. It would seem, therefore, that a previous history of pneumonia is more common among those cases complicated by collapse than would be expected. In addition, there were two patients among those included in this study in whose sputum tubercle bacilli were demonstrated during the acute pneumonia, but could not be demonstrated later. Both of these patients recovered and their lungs were apparently normal to physical examination and roentgen-ray except for a slight right apical fibrosis in one of them. Furthermore, in the cases presented in this paper and in those quoted, the right lung, and particularly the right upper lobe, was affected in far more than the usual proportion of cases. This circumstance and the fact that even in many of the cases in children reported in the literature there was a history indicating previous lung infection and the fact that lobes undergoing organization have become collapsed makes this a plausible contributory factor.

Jacobaeus, Lelander, and Westermark [40] have suggested another possible mechanism for the production of sudden massive atelectasis, namely a spontaneous spasm and contraction of a bronchus. They noticed appearance of massive collapse of a lobe within 10 minutes after lipiodal injections in certain normal individuals and explained it in this manner. Such a mechanism may be operative in pneumonia.

The cases reported in the literature and those presented here suggest that

atelectasis of the lung may be a frequent complication of primary pneumonia and may serve to explain unusual events or puzzling physical signs or a protracted course in otherwise uncomplicated cases. It may serve to explain the suppression of breath sounds early in the disease and later may be responsible for the signs often interpreted as resulting from thickened pleura or small amounts of fluid in the pleural cavity which cannot be verified by thoracentesis. It may be an important factor in the conditions variously known as unresolved pneumonia, delayed resolution, or organizing pneumonia and contribute to a delay in healing of empyema cavities. The condition may also serve to explain certain sudden episodes of acute dyspnea and sudden deaths occurring during the course of pneumonia or during the stage of resolution. In some instances such sudden deaths may be attributable to pulmonary infarction, a condition not infrequently seen at autopsy. Indeed, in case 1 this possibility is strongly suggested by the later appearance of phlebitis of the femoral vein. The failure of this patient to raise bloody sputum, the appearance of the characteristic physical and roentgenologic signs and the fact that the first evidence of phlebitis appeared only several days later make infarction a less likely explanation of the episode of dyspnea. Furthermore, in none of the cases showing massive atelectasis at autopsy was there evidence of pulmonary infarction.

There is no suggestion from the present cases or from those reported in the literature that atelectasis is an important factor in the pathogenesis of primary pneumococcus lobar pneumonia except possibly in certain cases where the onset of the disease occurs shortly after inhalation of foreign substances such as may occur after a vomiting spell. Such an assumption is not consistent with the definite occurrence of atelectasis during the disease and after the consolidation has already involved part or all of a lobe. The studies of Robertson and his coworkers also fail to uphold such an assumption either in the spontaneous disease in man [23] or in the experimental infection in dogs.[41]

Summary and Conclusions

1. A number of cases of massive atelectatic collapse of the lung complicating primary pneumonia were collected from the literature.

2. A group of 62 cases of primary pneumococcus lobar pneumonia in which this complication was noted in roentgenograms was presented.

3. A second group of 47 cases of pneumococcus pneumonias in which atelectasis of varying extent and due to a variety of factors was present at autopsy was also considered.

4. The significance of this complication was discussed.

5. The possibility of atelectasis should be borne in mind in cases of lobar pneumonia and may serve to explain certain otherwise puzzling physical findings, sudden attacks of dyspnea or an unusually protracted course.

6. The usual course of events in the characteristic case where the atelectasis complicates convalescence is somewhat as follows. A patient is acutely

ill with typical lobar pneumonia and begins to show gradual evidence of improvement, with lowering of fever and pulse rate and the appearance of moisture in the consolidated lobe indicating resolution. He is suddenly seized with intense dyspnea of short duration after which pleuritic pain, moderate fever, and leukocytosis recur, and the physical signs and roentgen-ray give evidence of elevation of the diaphragm with a shift of the heart, and usually the trachea also, to the affected side. The consolidated lobe may then show signs suggesting fluid or these signs alternating with those of solidification. When the upper lobe is collapsed, the breath sounds are intense and amphoric in character and, as moisture appears, suggest tuberculosis with cavitation. These signs may be present while fluid accumulates in the pleural cavity. The collapsed lobe reëxpands within a few days or weeks but organization and fibrosis may leave this affected lobe contracted.

In certain patients, particularly if they are markedly prostrated after a severe course, the signs of collapse may appear during convalescence without an explosive onset.

Collapse of varying degrees occurring during the acute stage of pneumonia may be manifested only by the signs suggesting fluid or by the evidence of displacement of the heart and trachea, or only by careful roentgenographic examination. In such cases the collapse, if it involves the affected lobe, is usually of short duration, evidence of solidification soon appears, and the course of the disease continues. If a previously uninvolved lobe is collapsed, the disease may extend to involve this lobe.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

THE EXOCRINE FUNCTIONS OF THE PANCREAS *

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EARLY in my career, interest in medical research problems was aroused through a fortunate association with Dr. Joseph H. Pratt of Boston. It was he who stimulated my investigations on the normal and the pathologic physiology of external pancreatic functions. The results of these investigations furnish the subject matter of the present dissertation.

Important studies on the rôle of the pancreas in digestion began with the work of Claude Bernard,[1] who showed that the pancreatic juice was essential to the process of digestion. Other physiologists of that time were, however, unable to confirm Bernard's observations,[2] and although many further careful investigations of the digestive function of the pancreas were reported by various observers, especially between the years 1890 and 1911,[3] the rôle of the pancreas in digestion remained an unsettled question until the studies of Pavlov.[4] Pavlov worked with dogs, in which animals he produced the fistulae which bear his name. By means of a fistula he was able to obtain pure pancreatic secretion, in which he demonstrated the presence of proteolytic, amylolytic and lipolytic enzymes. In later years Pratt [5] and still later McClure and Pratt [3] convincingly confirmed Bernard's observations that excluding pancreatic secretion from the intestines of dogs was immediately followed by lack of absorption of gross amounts of ingested foodstuffs.

In 1902 Bayliss and Starling [6] published their observations on the factors concerned in stimulation of external pancreatic secretion. From these observations they postulated the attractive theory that there exists a substance in the intestinal mucosa, designated as prosecretin, which is converted into another substance designated as secretin by action of hydrochloric acid coming from the stomach. They further postulated that the secretin thus formed was absorbed and carried through the blood stream to the pancreas, and after reaching that organ excited its external secretion. The studies of the many observers who have confirmed the experimental observations of Bayliss and Starling have been correlated and are critically presented in a publication of Farrell and Ivy.[7] Farrell and Ivy working with dogs also studied the effects on the enzymic concentrations of the secretions of a pancreatic transplant of administering different types of foodstuffs. From the results of these studies, together with those derived

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from the critical review of the work of Bayliss and Starling and subsequent experimentors, Farrell and Ivy [7] in 1926 confirmed the conclusion previously expressed by the present author [8]; which was that all the studies mentioned established the highly important physiological facts that (1) stimulation of the external secretion of the pancreas is of humoral origin, although the exact mechanism remains unsettled, (2) ingestion of food is followed by the secretion of pancreatic juice, and (3) the external secretion of the pancreas plays an essential rôle in digestion. Since this publication in 1926 Ivy [9] has succeeded in making a preparation from dogs' duodenal mucosa which he considers contains a hormone possessing the physiological properties ascribed to secretin. This work will be discussed later.

All of the investigations summarized in the foregoing paragraphs have been carried out on lower animals. In how far the results are applicable to man can be determined only by actual observations on human subjects. However, there is pathological evidence confirming the importance of the external pancreatic secretion in man; for example, disease which excludes pancreatic juice from the intestines of man is known to be accompanied by marked disturbances in the digestion and absorption of food. Various investigators have studied pancreatic secretions obtained from operative fistula in man. As the result of such a study Glaessner [10] found that the amount of pancreatic juice secreted was greatly augmented by food. Wohlgemuth [11] obtained pure pancreatic juice from a traumatic fistula in a human subject. Other than for the presence of the fistula, the subject's physical state was apparently normal. These studies showed that the ingestion of food consisting largely of fat brought about pancreatic secretion showing the greatest degrees of all types of enzyme action while the secretion following a carbohydrate meal showed the least. On the other hand, carbohydrate meals were followed by the secretion of the largest volumes of pancreatic juice, while fatty foods produced the least. Mocquot, Joltrain and Laudat [12] also found that carbohydrate food produced the greatest amount of pancreatic juice, but that a meat meal was followed by the least. Thus the results of these observations showed the existence of a relation between the kinds of foodstuffs ingested and the amounts of pancreatic juice secreted, and also the concentration of enzymes found in this juice. Kahn and Klein [13] also found that "There was a different rate for the secretion of the various enzymes and therefore a different rate for the discharge of the total amounts at one time, with corresponding variation in the frequency of renewal of the supply of enzymes of the gland." Wohlgemuth [11] and Mocquot, Joltrain and Laudat [12] observed intermittent secretion of pancreatic juice through the fistula, while von Friedrich [14] observed continuous secretion by his patient. Neither these observers nor Poljak [15] were able to demonstrate a relationship between the type of foodstuffs fed and the degree of concentration of the enzyme specific for that kind of food.

The studies on pancreatic secretion of man discussed were all carried out on subjects in more or less pathologic physical states, while the experi-

mental methods employed are open to criticism. Nevertheless, the findings show that in man, as well as in lower animals: (1) Ingestion of food is followed by the secretion of pancreatic juice, and (2) the external secretion of the pancreas plays an important rôle in digestion. These findings are obviously of great importance. Nevertheless, they do not establish the mechanism which stimulates the secretion of pancreatic juice nor the conditions under which intestinal digestion actually occurs in the living normal man. It is generally accepted that the end products of intestinal digestion in man are the same as those in lower animals; that is, carbohydrates are converted into monosaccharides, fats into soap and glycerol, and proteins into amino-acids, and that these end products are absorbed as such. However, it should be noted that it was not until the work of Folin [16] and of Van Slyke [17] that the absorption from the gut of the end products of protein digestion was established. It is only fair to add that all the phases of the various processes involved in the digestion and absorption of both proteins and fats are not yet fully established.

There are available but comparatively few studies on the physical and chemical conditions under which intestinal digestion occurs in man. Practically the only studies on the physical chemistry of intestinal digestion in the living normal human subject are those of McClendon et al.,[18] Hume, Denis, Silverman and Irwin [19] and that of the present author and his co-workers which will be discussed later. In fact many of the conditions affecting enzyme action were not established until the publication of the work of Sörensen [20] in 1909. This work permitted the development of reliable methods for indirectly quantitating enzymes present in pancreatic juice, first by McClure [21] and then later by Willstätter [22] and Ivy.[9, 23] These methods, the roentgen-ray, electrometric apparatus, the duodenal tube, together with advances in physical chemistry and biochemistry, permitted the development of procedures and methods for studying digestion in the living man. The most extensive systematic studies of this subject were carried on first by McClure and co-workers [24] and later by Christiansen of Copenhagen.[25] Several studies on man have been made by Chiray [26] and less extensive observations by other investigators; these studies will be discussed later. The clinical importance of all these various studies is due primarily to the objective demonstration of phenomena occurring in normal human subjects which will permit comparisons with those occurring under similar experimental conditions in abnormal subjects. The explanations of the mechanisms of functional activities producing the phenomena are of only indirect value in the actual use of the tests in medical diagnosis. This indirect value lies in the fact that usually, but not always, the more nearly correct the physiological basis for a clinical test or procedure the more reliable are the results for diagnostic purposes. Thus, the interpretations of results of investigations made for clinical purposes may be, indeed often are, radically different from those which are of value in the medical sciences.

Long experience in clinical medicine, clinical research and investigations in pure science have led the present author to conclude that the investigator who has not had a considerable experience in the actual practice of medicine rarely is capable of the type of interpretation required for purposes of clinical diagnosis. In relation to human medicine both physiology and pathologic physiology may be, therefore, approached from two viewpoints. The discussion of the physiology and pathologic physiology of the pancreas, which follows, is from the viewpoint of the practitioner of medicine.

In pursuit of clinically applicable studies of the physiology of intestinal digestion in normal man suitability of analytical methods and proper experimental procedures and conditions are of essential importance. Such methods, procedures and conditions were developed by the present author and co-workers and on them depends very largely the reliability of the studies whose discussion follows.

One of the problems was whether or not reliable means could be developed for demonstrating pancreatic stimulation by examination of duodenal contents. The measure of pancreatic activity chosen by the present author was that of enzymic concentration, while Christiansen [25] selected the quantity of enzymes secreted. The results obtained by both of us showed that stimulation of the enzymic function of the pancreas could be demonstrated by examination of duodenal contents obtained under suitable experimental conditions and analyzed by proper methods.

The Effects of Foodstuffs on Concentration of Pancreatic Enzymes

The present author's studies [27] showed that pancreatic juice containing variable concentrations and amounts of enzymes is obtainable from the normal human duodenum during the fasting state. It was further found that following cessation of stimulation of the pancreas the juice secreted again assumed the characters of that obtained during the fasting state. Stimulation was characterized by a much greater average concentration of the three types of enzymes and by a greater uniformity in the degrees of enzymic concentrations.

Observations were made to determine possible variations in the concentrations of the various enzymes during different periods in which the secretion of pancreatic juice was stimulated by ingested foodstuffs. For this purpose normal subjects were fed pure protein, and duodenal contents were collected over relatively short intervals during the period of pancreatic stimulation. This study showed that in different fractions of duodenal contents collected from the same subject the concentrations of the same type of enzyme remained fairly uniform. Further observations on the uniformity of enzymic concentrations were made on specimens of duodenal contents collected over hourly periods from normal subjects. The meals were of such size that the minimum emptying time of the stomach as determined

by fluoroscopic examination was more than four hours. This permitted the collection of not less than four specimens from each subject. The study showed that each of the several types of enzyme varied moderately in the degrees of its concentration in the different hourly specimens of duodenal contents from the same subject, but that there was no regular manner in which the variations occurred; that is, there was no constant systematic increase in the enzymic concentrations throughout the period of pancreatic stimulation.

Studies were made to ascertain whether the greatest degree of concentration of a given enzyme occurred in the presence of a meal composed of a type of foodstuff corresponding to its substratum. For this purpose normal subjects were given at different times a meal composed of various pure proteins, fats or carbohydrates. The results showed conclusively that no one kind of pure foodstuff stimulates the greatest concentration of its specific type of enzyme. Christiansen [25] made similar findings in relation to the amounts of enzymes secreted under comparable experimental conditions. In addition to the studies discussed, a series of normal subjects was subjected to intraduodenal administration of pure foodstuffs.[28] The latter were cottonseed oil, special preparations of casein and of beef furnished by the Arlington Chemical Company and dextrose. The oil was mixed with water and the other substances dissolved in water and then introduced into the duodenum through the duodenal tube. Foodstuffs thus administered produced in the same subject enzymic concentrations of duodenal contents entirely comparable to those obtained after their oral administration. After intraduodenal administrations the bile and gastric fractions of the collected duodenal contents were analyzed as well as the pancreatic fraction. The findings apparently eliminated the possibility of the volume of one fraction masking the effects of the other fractions through dilution, because the increases or decreases in the analytical figures rarely failed to coincide.

The foregoing studies show: (*a*) There is a period following the ingestion of foodstuffs during which definitely increased concentrations of pancreatic enzymes are demonstrable in the pancreatic juice collected from the duodenum of man; this period is the result of stimulation of the activity of the external function of the pancreas. During this period of stimulation the concentration of each type of enzyme varies much less than in duodenal contents collected either before or after stimulation. Christiansen found an increase in the amounts of enzymes secreted during this period.

(*b*) In duodenal specimens collected over succeeding periods during which pancreatic stimulation is in process the enzymic concentrations remain fairly uniform in degree.

(*c*) The greatest degree of concentration of a given enzyme is not governed by the type of foodstuff corresponding to the specific substratum in which the enzyme acts. However, the degrees of concentration of all

types of pancreatic enzymes are related to the kind of foodstuff fed, oil giving the greatest degree and carbohydrates the least. Christiansen also found well defined relationships between the amounts of enzymes secreted and the type of foodstuff administered.

In relation to clinical diagnosis these findings are important not because of the physiological implications, which will be discussed later, but because they furnish norms with which the findings obtained from pathological subjects can be compared.

Effects of Inorganic Substances on Concentration of Pancreatic Enzymes

Having established the rôle played by foodstuffs on the external secretory activity of the pancreas it was considered of equal importance to study the effects of representative inorganic substances. The substances chosen were distilled water, chemically pure hydrochloric acid, phosphoric acid, sodium phosphate and magnesium sulphate.

Comparative studies [7, 8, 28, 29] of the degrees of enzymic concentration were made in duodenal contents derived from the fasting duodenum, after the ingestion of tap water and after drinking weak cornstarch solution. For this purpose the fasting duodenal contents were collected over periods of 30 minutes from normal subjects, then 50 c.c. of tap water were given and the contents collected for two hours, in fractions of one hour each. The enzymic concentrations of the two fractions were comparable. The results representative of those obtained from this comparative study are outlined in the following table. To the table are added the figures representing the enzymic concentration of duodenal contents collected after the ingestion of a mixture of olive oil and tap water. The experiments with the oil feedings and those with the fasting duodenum and tap water feedings were made on separate days.

Table I

Enzymic Concentrations of Duodenal Contents Collected from the Fasting Duodenum and after the Ingestion of Tap Water, or of Cornstarch Solution or of Olive Oil

Enzymic Concentration			Food Ingested
Proteolytic in mg. N.P.N.	Lipolytic in c.c. N/10 NaOH	Amylolytic in mg. glucose	
1.8	0.5	0.3	Fasting duodenum
5.7	3.5	2.6	25 c.c. of olive oil and 25 c.c. tap water
2.7	0.0	0.0	50 c.c. 0.5% cornstarch
1.5	0.1	0.0	50 c.c. tap water

In the above table comparison of enzymic concentrations of the contents of the fasting duodenum with those found after drinking water shows that after the ingestion of water or weak cornstarch solution the degrees of con-

centration of the various enzymes present in the duodenal contents are comparable with those present in the fasting contents. However, after the ingestion of olive oil, the degrees of action of all these various enzymes were increased in the duodenal contents of each subject.

Comparative studies were made of enzymic concentrations of duodenal contents obtained after the ingestion of olive oil and of various hydrochloric acid mixtures. The determinations were made in duodenal contents from normal subjects. Results representative of those obtained in a series of experiments are outlined in the following table.

TABLE II

Enzymic Concentrations of Duodenal Contents Obtained after the Ingestion of Hydrochloric Acid and Olive Oil

Enzymic Concentrations			Food Ingested
Proteolytic in mg. N.P.N.	Lipolytic in c.c. N/11 NaOH	Amylolytic in mg. glucose	
4.3	1.2	1.2	100 c.c. N/10 HCl and gum arabic
2.2	0.0	0.2	60 c.c. N/10 HCl and gum arabic
2.7	0.7	1.4	50 c.c. N/10 HCl solution
5.7	2.5	2.5	25 c.c. each of olive oil and water

Study of the table shows that the greatest enzymic concentrations were obtained in duodenal contents derived after the ingestion of olive oil, and that acid was a much less potent stimulant. The latter acted comparably to water. This is to be anticipated because ingestion of water stimulates the production of acid gastric secretion. Observations in which phosphoric acid was used instead of HCl gave results comparable to those described for the latter acid.

Studies [28] were made on five normal subjects of the comparative stimulative effects of foodstuffs, HCl and $MgSO_4$ solutions in the secretions of pancreatic juice. These subjects were given, in aqueous suspension, 100 c.c. of 50 c.c. pure cottonseed oil, or a solution of one of the following substances, 50 grams of fat-free beef peptone, 50 grams pure dextrose, 8 grams of $MgSO_4$ crystals or N/40 HCl. Results representative of those obtained are outlined in the following table.

The findings of this study, represented in table 3, show that magnesium sulphate is a more potent stimulant to the secretion of pancreatic enzymes than is HCl solution or dextrose. They also clearly show that inorganic substances, including HCl, are less potent stimulants to the secretion of pancreatic enzymes than are fats or protein foodstuffs.

The studies which have been briefly described show that the inorganic substances, hydrochloric acid, phosphoric acid and water, are weak and inconstant stimulants to the flow of pancreatic enzymes. Magnesium sul-

TABLE III

Minimum and Maximum Concentrations of Enzymes and Chlorides of Duodenal Contents before and after Intraduodenal Administration of Cottonseed Oil, Beef Peptone, Dextrose, HCl and $MgSO_4$

Test Meal	Pancreatic Enzyme Concentrations						Pepsin Concentration		Chloride Concentration	
	Trypsin		Lipase		Amylase					
	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum
Fasting	1.3	4.2	0.2	1.2	1.9	3.6	0.7	1.0	5.9	6.4
$MgSO_4$	3.9	4.6	0.8		0.9	1.4	0.9	1.1	5.2	7.0
HCl	3.8		0.8	1.0	0.7		0.7		4.2	
Dextrose	3.3		0.5		0.7		1.6		4.1	
Peptone	9.5		1.0		3.6		2.0		8.5	
Oil	5.7	8.6	1.2	1.5	4.0	4.5	0.6	1.0	5.2	7.0

phate was a more constant and potent stimulant than were these other substances; although it fails to stimulate in about 20 per cent of normal subjects. At the best, magnesium sulphate was a much less reliable and less powerful stimulant than either fat or protein foodstuffs.

The action of these inorganic substances on the exocrine pancreatic function is comparable to that described by Ivy [9] after parenteral administration of a substance designated purified secretin. In relation to clinical medicine the studies on inorganic substances are important because they show that such compounds are not satisfactory stimulants when the pancreatic fraction of duodenal contents is examined for diagnostic purposes.

ALKALI SECRETORY ACTIVITY OF PANCREAS

The studies which have been discussed showed that different types of stimulants reacted differently on the external enzymic functions of the pancreas. Obviously, these findings explain the logic of studying the effects of various types of stimulants on the alkali secretory activity of the pancreas. For this purpose pH and buffer values of duodenal contents were determined.[30] All pH determinations were made electrometrically. The buffer values were determined by titrating duodenal contents either with tenth normal hydrochloric acid or with sodium hydroxide solution, according as to whether the original material was alkaline or acid. This was accomplished by bringing a definite quantity of the duodenal contents to the neutral point by the addition of standard acid or alkali; the pH values being determined initially and the neutral point evaluated by further potentiometric comparisons, after addition of successive portions of titration solutions. Studies were first made on duodenal contents collected from normal subjects in the fasting state, and then after ingestion of tap water. The pH values obtained during fasting were 6.0 to 8.1 and after water drinking were 7.6

to 8.3; which indicates that water drinking caused some stimulation of alkali secretion. After these preliminary studies the subjects were fed pure foodstuffs or mixtures of them. Duodenal contents were collected during the period of stimulation of the pancreatic juice and pH determined. It was found that duodenal contents derived after the ingestion of olive oil or of arrowroot starch were alkaline (pH above 7); the pH varied from 7.2 to 8.1. On the other hand, duodenal contents collected after ingestion of the protein, edestin, or the mixture of foodstuffs containing edestin were acid (pH below 7); the pH varied from 3.2 to 6.7. The correctness of these findings has been verified by others.[18, 19, 31, 32, 33] The buffer values of the duodenal contents obtained after administration of foodstuffs were surprisingly uniform. Such uniformity indicates that the physical chemical factors governing the buffer conditions were approximately the same in all specimens of duodenal contents; i.e., the findings indicate that the various types of food substances had about the same stimulating effect on the production of buffer substances. Obviously, this finding indicates that foodstuffs stimulate the alkali secretory activity of the pancreas in a manner differing from their stimulation of the enzymic activities.

The determinations of the pH values discussed above do not afford data concerning the rapidity with which gastric chyme is neutralized within the duodenum. In order to obtain such data [8] duodenal contents for pH determinations were obtained by aspiration from the first portion of the duodenum; the metal tip was either just beyond the distal end of the sphincter, or within the sphincter. Collections were made over periods of a few seconds to several minutes, depending on the time necessary to collect a quantity sufficient for potentiometric purposes; about 5 c.c. A second duodenal tube was placed in the stomach in order to prove that the ingested meal gave rise to an active flow of acid gastric juice; the acidity being determined by titration and electrometrically. The substances fed were olive oil and N/10 HCl. These studies showed that the acidity of gastric chyme is neutralized the instant it reaches the duodenum and that the neutralization occurred in the region of the pyloric sphincter. The neutralization may be compared to that produced by pouring an acid solution onto the surface of an alkaline fluid with diffusion downward.

Independent stimulation of the two types of pancreatic secretions, alkali and enzymic, was studied further. For this purpose enzymic concentrations of duodenal contents were determined after the ingestion of olive oil and various mixtures of hydrochloric acid. The results of these studies showed that only an indifferent relationship existed between the enzymic secretory function of the pancreas and the alkali secretory function. The independence of these two secretory activities is also maintained by other observers.[23, 34, 35] The studies on the alkali secretory function of the pancreas furnish normal findings with which those on abnormal subjects may be compared.

Mechanism of Pancreatic Stimulation

The foregoing findings which have been discussed furnish data not only applicable to clinical studies but also relating to the factors concerned in stimulation of the external secretory functions of the pancreas. Such stimulation is usually attributed by physiologists to the hypothetical hormone designated secretin. Bayliss and Starling [6] proposed this theory on the basis of two observations. First, they found that when acid is applied to a denervated loop of the upper jejunum the pancreas secretes. Second, they also found that acid extracts of the duodenal and jejunal mucosa contained a substance called by them, "secretin," which excites the pancreas to secrete when injected intravenously. However, substances possessing the action of "secretin" have been found in many animal tissues other than duodenal and jejunal mucosa and its extraction with hydrochloric acid might very well form various compounds (due to decomposition of proteins, etc.) whose parenteral administration would stimulate the secretion of pancreatic juice. A concise critique of the animal experimentation relating to hormonal stimulation of the pancreas is reported by Farrell and Ivy [7]; together with the observation that they were able to stimulate the secretion of pancreatic juice by a denervated autotransplant of the pancreas in the dog. Their conclusion confirms the opinion of the author that the work of Bayliss and Starling indicates humoral stimulation but not necessarily hormonal stimulation. In more recent studies Ivy [9] produces stimulation of the flow of pancreatic juice in dogs and in man by the parenteral administration of a preparation designated as a purified secretin. These findings apparently establish a humoral stimulation of the exocrine functions of the pancreas in both lower animals and in man.

The establishment of the chemical (humoral) stimulation of the exocrine functions of the pancreas is of sufficient importance to justify the large amount of experimentation carried on by various observers during the past 32 years. However, merely because a parenterally administered substance stimulates pancreatic secretions does not prove the existence of a hormonal (secretin) mechanism of such stimulation. Realizing this, Ivy made further investigations [9] in which he found that his purified secretin and also various foodstuffs failed to influence the enzymic concentrations of pancreatic juice of dogs. Obviously, these findings favor the correctness of the hormonal (secretin) stimulation in dogs. However, although Ivy's purified secretin [9] did not affect the concentrations of pancreatic enzymes in man, the investigations of the present author and others have unquestionably established that such concentrations are definitely affected by various foodstuffs. These reported differences suggest that there possibly exist differences in the mechanisms of pancreatic stimulation in dog and man. It would be logical to postulate that the carnivora require only a restricted type of pancreatic stimulation since protein is the predominant foodstuff, while omnivora might require more complicated mechanism because of the various

elements habitually entering into their diet. Another important fact is that the experimental observations have always been made on animals whose physiological states have been drastically modified. These considerations make it seem hazardous to conclude from experimental data now available that the mechanisms of stimulation of the exocrine functions of the pancreas in man are necessarily similar or indeed comparable to those in lower animals.

There are various studies made by the author and Christiansen the results of which are not compatible with the secretin theory of stimulation of the pancreas. It will be recalled that the secretin theory postulated an acid state of duodenal contents. However, studies discussed above show that the duodenum during digestion is either alkaline or the amount of free HCl is not more than a trace. Certainly hydrochloric acid could not have played a rôle in the stimulation of the pancreas in the author's patient with achylia gastrica; the gastric contents were kept alkaline by mixing sodium hydroxide with the foodstuffs fed. These findings negative the application of the secretin theory, as usually described, to man. Measuring the production of enzymes in terms of enzymic concentrations shows such production to be governed by the type of stimulant administered. Were pancreatic stimulation in man the result of only the one substance, secretin, the consistent variations which have been found for different types of stimulants would not be anticipated.

Both Ivy [9] and Chiray [26] found that the parenteral administration of substances designated by them as purified secretin stimulated an increase in the amount of pancreatic juice secreted by normal men. Chiray also found an increase in the concentration of enzymes, while Ivy did not. The difference in findings is logically explained as due to differences in the substances administered. These findings are evidence favoring the correctness of the conclusions drawn independently by the present author and by Christiansen, which is that the alkali and enzymic activities of the pancreas are independent functions. The author's studies [8] of this problem were made on normal young men. The subjects were fed water, hydrochloric acid, olive oil mixed with hydrochloric acid, and olive oil mixed with water. Two tubes were used simultaneously; the tip of one entering the duodenum and the tip of the other remaining in the stomach. The latter tube permitted it to be shown that the contents of the stomach were actively acid throughout the experimental observation periods. Throughout these periods gastric acidity was titrated and electrometric pH determinations were made of the gastric and duodenal contents together with estimations of the concentrations of the pancreatic enzymes. These findings showed that water and hydrochloric acid solutions stimulated the secretion of alkali by the pancreas but produced no demonstrable effect on the concentration of enzymes. On the other hand, the olive oil meals stimulated both the alkali and enzymic fractions of pancreatic juice, the gastric contents being actively acid. These

findings indicate that the two exocrine pancreatic functions react differently. Christiansen [25] investigated the subject with unique experimental procedures. From his studies he concluded that the secretion of alkali and the secretion of enzymes represent independent functions.

Pathologic Physiology of External Pancreatic Function

The experimental findings and their relation to the mechanisms of external pancreatic functions which have been discussed furnish a basis for the study of abnormal pancreatic conditions, whether functional or organic. In making such studies propriety of experimental methods and procedures is of essential importance. Those developed and used by the present author will be discussed in connection with the considerable number of other procedures which have been proposed for the purpose of eliciting evidence of pancreatic involvement. Critical review of them demonstrates that they are designed to show functional disturbances in the pancreas either directly or indirectly through the secondary effects on metabolism. They may be classified as follows:

I. Test for demonstrating the secondary effects of pancreatic function
  A. Effect on carbohydrate metabolism.
    1. Glycosuria
      (*a*) Dynamic
      (*b*) Potential
    2. Cammidge pancreatic reaction [37]
  B. Unclassified effect on metabolism
    1. Loewi mydriasis test [38]
  C. Effect on alimentation
    1. Steatorrhea and percentage of undigested fats [3, 39, 40]
    2. Azotorrhea and creatorrhea [41, 42]
    3. Urinary ethereal sulphates

II. Direct tests for pancreatic function
  A. The estimation of the concentration of pancreatic enzymes in vitro (quantitative)
    1. Estimation in excreta
      (*a*) Trypsin in feces [43, 44, 45]
      (*b*) Diastase in feces [46, 47, 48]
      (*c*) Lipase in urine [49]
      (*d*) Diastase in urine [47]
    2. Estimation in gastric contents
      (*a*) Trypsin, diastase and lipase after an oil meal [50, 51]
    3. Estimation of enzymes in duodenal contents
    4. Estimation in blood
      (*a*) Diastase [47, 52, 53]
      (*b*) Lipase [54, 55]

B. The estimation of the concentration of pancreatic enzymes in vivo

1. Keratin coated capsules containing methylene blue [56]
2. Glutoid capsules of Sahli containing iodoform [57]
3. Nucleus test of Schmidt,[58] and the modifications of Einhorn,[59] and Kashiwado [60]

Descriptions of these various tests are found in the encyclopedic work of Weiss [61] and in other publications.[39, 41, 42, 62]

Of the above tests but few have proved to be of practical value. Steatorrhea, azotorrhea and creatorrhea occur in the presence of advanced disease of the pancreas. In the presence of complete exclusion of pancreatic juice the nucleus test may still be positive. Of the various examinations of substances in the blood the most efficient [63] is the test for lipase devised by Cherry and Crandall.[55] In relation to lipase in the blood, it is of interest to note the work of Boldyreff.[64] This investigator has concluded from experimental observations that the external pancreatic secretion furnishes enzymes to the blood. Both Boldyreff [64] and Oelgoetz [65] attribute great importance to this phenomenon. However, neither of these observers has given consideration to the rôle played by the liver in destroying pancreatic enzymes reaching it in the portal blood, which phenomenon is discussed by Fischler.[66] Examination of the pancreatic moiety of duodenal contents furnishes the most useful information concerning the functional state of the pancreas. The reliability of such examinations depends (*a*) on the correct use of the duodenal tube, (*b*) on procedures which insure the collection of representative specimens of duodenal contents, (*c*) on the use of a stimulant which will uniformly cause secretion of pancreatic juice and (*d*) on analytical methods incorporating the necessary physiochemical principles. The present author has developed a system of duodenal analysis [24] which incorporates all these requirements. Sufficiently large numbers of normal and pathological subjects have been studied to establish the status of this system. In brief the method consists of giving the duodenal tube with the subject in the fasting state, and verifying the position of the tip of the tube by fluoroscopy. Cream or oleic acid is used to stimulate pancreatic secretion; and a specimen is then collected which is representative of the duodenal contents during the period of such stimulation. The specimen is analyzed for enzymic activities by the methods devised by the author; these incorporate the necessary physiochemical principles. Willstätter [22] and also Ivy [9] have developed reliable analytical physico-chemical methods for estimating enzymic activities. The status of the results obtained from the author's system of duodenal analysis in relation to clinical diagnosis was established by the study of large numbers of patients representing a considerable variety of diseases. Results representative of those obtained in patients suffering from organic pancreatic affections are outlined in the following tables.

TABLE IV

Representative Duodenal Enzymic Concentrations in Pancreatic Disease

Subject	Proteolytic non-protein nitrogen mg.	Lipolytic N/10 NaOH c.c.	Amylolytic glucose mg.	Diagnosis
Normal controls	2.0	1.0	1.0	
4*	5.0	0.2	0.4	Acute pancreatitis convalescing
	1.9	0.7	1.9	
3*	1.1	0.3	0.5	Chronic pancreatitis
	0.8	0.3	0.3	
2*	0.0	0.2	2.0	Cancer head of pancreas
1*	2.5	1.6	2.0	Cancer of body and tail of pancreas

* Laparotomy.

The effects of pancreatic disease on the enzymic concentrations of duodenal contents, demonstrated by studies comparable to those outlined in table 4 together with those reported by other investigators [67] may be summarized as follows:

Extensive involvement of the pancreatic parenchyma, due to acute pancreatitis or less extensive pathologic lesions accompanying chronic pancreatitis, is associated with a decrease below the minimum normal limits of at least two of the three types of enzymic concentrations in the duodenal contents. It is possible that the diminution in enzymic concentrations in some of these cases is due, in part, to obstruction to the flow of pancreatic secretion by the pathologic process, as well as to actual destruction of pancreatic parenchyma.

Cancer of the head of the pancreas produces a marked decrease in enzymic concentrations; although extensive carcinomatous involvement of the pancreas, not involving the head or the duct of Wirsung, does not demonstrably affect the enzymic concentrations of duodenal contents.

Slight involvement of the pancreatic parenchyma, when due to acute pancreatitis or pancreatic cyst, does not affect the enzymic concentrations of the duodenal contents.

The functional state of the pancreas, as reflected in changes in enzymic concentrations in duodenal contents, was investigated [68] in patients suffering with diseases of the liver or gall-bladder. In chronic cholecystitis, with or without gall stones, about 50 per cent of the cases showed slight abnormality in pancreatic enzymic function. This was most often expressed as a diminution in the concentration of lipase. The presence or absence of jaundice exerted no demonstrable influence on pancreatic function. Comparable evidence of pancreatic functional disturbance was demonstrated in 95 per cent of the patients who had undergone cholecystectomy. Calculous obstruction of the ampulla of Vater will produce low enzymic concentrations. These findings have been verified

by others.[67, 69] Very abnormal enzymic concentrations were also found in acute cholecystitis. However, normal enzymic concentrations were found in cancer of the bile ducts which did not involve the pancreatic ducts. Mild disturbance of pancreatic function was found in 70 per cent of patients with cirrhosis of the liver and in 50 per cent of patients with toxic jaundice. Only about 16 per cent of patients with uncomplicated duodenal ulcer gave evidence of mild pancreatic dysfunction.

The combined study of the pancreatic and biliary moieties of duodenal contents has been found of value in differentiating between benign and malignant causes for jaundice and in localizing the site of the lesions. The important findings in such differentiation may be outlined as follows:

Normal enzymic concentrations and no bile demonstrate that the lesion is in the biliary tract above the ampulla of Vater. If bile reappears after repeated instillation of magnesium sulphate solution into the duodenum it is highly probable that the obstruction of the biliary tract is of benign character. The more concentrated the bile that is obtained, the more probably benign is the lesion. But if bile does not reappear, the chance that the lesion is benign is much more remote.

Abnormal enzymic concentrations, with the initial presence of bile, especially if the bile is relatively concentrated, or if it reappears after intraduodenal instillation of magnesium sulphate solution, suggest benign obstruction in the region of the ampulla of Vater. In such cases the reappearance of bile may be accompanied by increase in enzymic concentrations.

Abnormal enzymic concentrations, when bile remains absent from the duodenum in spite of repeated intraduodenal administration of magnesium sulphate, suggest cancer of the head of the pancreas.

Duodenal contents grossly discolored with blood, with abnormal enzymic concentrations, and containing no bile denote cancer involving the head of the pancreas, common bile duct and wall of the duodenum.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

VITAMIN C AND INFECTION *

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INTRODUCTION

THE conception that scurvy has an important relationship to infection is far from new. In fact, some of the earliest descriptions of scurvy bear witness to this relationship and account for the fact that scurvy was often considered an infectious disease. Echthius, whose comments on scurvy were published in 1585,[1] is referred to by James Lind [2] as follows: "Echthius seems to be the first who gave rise to the opinion of its being a contagious or infectious *lues*. He was led into that mistake by observing whole monasteries who lived on the same diet, and in the same air, at once affected with it, especially after fevers; which no doubt might become infectious in close and confined apartments. He imagined, therefore, that a scurvy might in a manner be the *crisis* of a fever, which as such he deemed contagious." This relationship was more clearly recognized by Maynwaringe,[3] a century later, who wrote: "That Feavers and Scurvy do commute and complicate, daily experience doth manifest to Learned *Physicians*, that are *critical* observators: and those intermitting *Feavers*, called *Agues*, which are looked upon and accounted by the vulgar and unknowing, as trivial slight diseases; and, as I have heard some say, *An Ague in the Spring is as good as Physick*: but they little consider what *ruine* these *Agues* bring to the best tempered bodies; what alteration and change they make in the *mass* of blood; seldom recovering its former state and purity, if they continue long and neglected: and at their cessation and departure you think all is done, the danger and the *prejudice* past, and you *in statu quo prius;* but now begins the *Scurvy* to act its part, slily and gradually to creep upon you, except by the advice of a skillful Physician, you raze out the *vestigia* of the former disease, *characterized* and *impressed* upon the *Viscera* for nutrition, by *alienating* their ferments from their genuine and *primitive* natures, from which *seminaries* the *Scurvy* will spout forth.

"Hereby you may perceive the succession and commutation of diseases, how one disease *introduceth* and is the *preludium* to another."

However faulty may have been the reasoning of the early commentators as to the fundamental cause of scurvy their observations on the effect of

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infections in precipitating the disease have been repeatedly confirmed. Time after time epidemics of scurvy have been seen to sweep through an inadequately fed populace on the heels of a contagious disease. As recently as 1917 this phenomenon was reported from the prison camps of the Central Powers.[4]

Of late years, improvement in the dietary of the poorer classes has been sufficient to make scurvy a relatively uncommon condition confined largely to infants, solitary living bachelors, alcoholics, and patients on certain rigid diets, such as for peptic ulcer. Even in individual cases, however, the influence of infection in unmasking a latent scurvy is often manifest. As Hess [5] has remarked, "Infection is the most important condition which may suddenly and precipitously induce scurvy."

The chemical isolation of vitamin C or ascorbic acid and the subsequent development of methods for its quantitation in plant and animal tissues have made it possible to study its metabolism in health and disease in a more exact way than hitherto. Vitamin C is a powerful reducing agent and its ability to reduce 2.6 dichlorphenol-indophenol under suitably controlled conditions has been shown to be highly specific.[6, 7] With this dye vitamin C can be titrated directly in the urine or in the protein-free filtrate of blood serum or plasma.

It has been observed that in normal individuals the blood serum level of ascorbic acid is between 0.7 and 2.5 mg. per 100 c.c., and even within this normal range differences can ordinarily be accounted for by differences in dietary intake of vitamin C.[8] Elimination of vitamin C from the diet has been observed to be followed by a gradual fall in the blood level of the vitamin until it reached a value as low as 0.2 mg. per 100 c.c.[9]

The urinary excretion of vitamin C is in the normal healthy subject dependent upon the dietary intake.[9, 10, 11] Although observations on the serum level or urinary output of vitamin C in infection have been few and contradictory,[12-21] experimental evidence has been accumulating that there is an increased demand for the vitamin in infection. Rinehart [20] has shown that this is the case in active rheumatoid arthritis and rheumatic fever, and Heinemann [21] has confirmed this in other infectious diseases. However, studies of the vitamin C metabolism in a large series of cases with infection are lacking. The purpose of the observations reported here was to seek evidence in regard to the effect of infection on the vitamin C metabolism by estimating the blood ascorbic acid in a large group of hospital patients and controls, and by "balance" experiments in a few patients with infections.

Methods

The reduced ascorbic acid in the blood serum was determined by the method of Taylor et al.[22] Repeated estimations have shown an accuracy of 0.2 mg. per 100 ml. of blood serum. The data presented were collected from 165 individuals representing a cross section of the hospital population

including, as controls, members of the staff and technicians, as well as patients without infections.

These individuals have been arbitrarily divided into four groups. Group I consists of individuals free from infection who had been on a diet containing some fresh fruit or green vegetables. Group II consists of patients with infections who had been on a diet containing some fresh fruit or green vegetables. Group III consists of patients free from infection who had been on diets lacking in fresh fruits and green vegetables. Group IV consists of patients with infections who had been on diets lacking in fresh fruits and green vegetables.

The first group ("adequate" vitamin C intake without infection) was composed of 43 individuals from all walks of life, the majority of whom were ward patients in the hospital. The average serum level of ascorbic acid in this group was 1.31 mg. per 100 c.c. with a range from 0.51 to 2.42 mg. per 100 c.c.

The second group ("adequate" vitamin C intake with infection) consists of 66 patients suffering from various infections such as lobar and bronchopneumonia, acute upper respiratory infection, tonsillitis, rheumatic fever, acute gonorrheal arthritis, pyelitis, cystitis, pulmonary and pleural tuberculosis, bronchitis, lung abscess, malaria, acute catarrhal jaundice, staphylococcus abscesses, typhoid fever, streptococcus septicemia, and osteomyelitis. No patient was included who did not exhibit either fever or leukocytosis. The average level of serum ascorbic acid in this group was 0.64 mg. with a range from 0.10 to 1.19 mg. per 100 c.c. This is about one-half the average value found in the normal group. No correlation between the severity or etiology of the infection and the level of ascorbic acid in the blood was noted except that all of the cases of uncomplicated pyelitis or cystitis, five in number, had normal values. In 10 cases of active rheumatic fever included in Group II the average value was 0.48 mg. per 100 c.c. with a range from 0.10 to 0.85 mg. per 100 c.c., essentially the same as for the group as a whole.

The third group ("inadequate" vitamin C intake without infection) consists of 27 patients. In these the average serum ascorbic acid value was 0.48 mg. with a range from 0.11 to 1.26 mg. per 100 c.c.

The fourth group ("inadequate" vitamin C intake with infection) consists of 29 patients. In these the average value was 0.47 mg. of ascorbic acid per 100 c.c. with a range of from 0.21 to 0.91 mg. per 100 c.c., essentially the same as for Group III. (Figure 1.)

Clinical signs of scurvy such as spongy, bleeding gums or spontaneous hemorrhages into the tissues were not observed in either Group I or Group II but were noted in ten patients in Group III and three patients in Group IV. There was no significant difference in the serum level of ascorbic acid between the patients with scurvy and those with equally poor diets without scurvy.

On encountering these results the question arises, "Could they not be due to lessened intake of vitamin C from lack of appetite or defective absorption associated with infectious disease?" In answer to this, it may be said that many of these patients were observed to be partaking of an adequate diet in the hospital, and in many the determination of serum ascorbic acid was done within a day or two of the onset of the disease before it would be expected that the effects of faulty absorption would become manifest.

A study of the vitamin C balance was carried out in four individuals with chronic infections: two patients with pulmonary tuberculosis, one with rheumatic fever, and one with lung abscess. Inasmuch as the observations in all four yielded essentially the same results only one case will be described in detail. T. W. was an elderly man with advanced pulmonary tuberculosis, who weighed 50 kilograms. Previous to entry to the hospital he had been

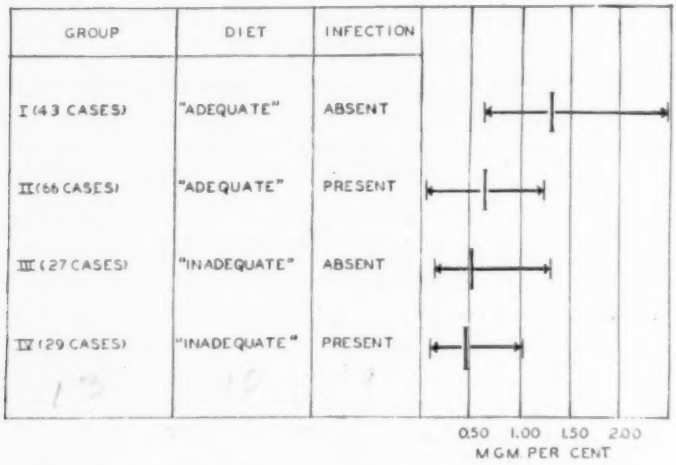

FIG. 1. Average serum ascorbic acid and range of values in various conditions.

on a diet containing raw fruit or cabbage several times a week. His clinical condition remained essentially unchanged throughout the course of the observations. During his stay in the hospital he was kept on a basal diet which contained no fresh fruit, tomato or cabbage; in other words, it was moderately low but not completely lacking in vitamin C. On admission the serum ascorbic acid was 0.30 mg. per 100 c.c. while the average total daily excretion into the urine was 3 mg., a very low value. These figures showed no essential change over a control period of three weeks. During the succeeding 10 days he was given on separate occasions one intravenous dose and two oral doses of one gram each of ascorbic acid. These large single doses of ascorbic acid were followed during the first 24 hours by an increased excretion of the vitamin in the urine amounting to 254 mg. after the intravenous injection, and 21 and 71 mg., respectively, after the oral administrations. During the second 24 hours on each occasion the urinary

excretion fell to its previous low values. At the end of this period the plasma ascorbic acid had risen to 0.95 mg. per 100 c.c. He was then given 500 mg. of ascorbic acid by mouth daily for four weeks. The response to this amount was shown by a prompt rise in the plasma ascorbic acid to 1.31 mg. per 100 c.c., accompanied by a marked increase in the urinary excretion to from 200 to 300 mg. per day. Ascorbic acid administration was then discontinued for four weeks and there was a rapid fall in the plasma ascorbic acid to its preëxisting low level. At this point increasing doses of ascorbic acid were given by mouth beginning with 100 mg. per day for 13 days, then 200 mg. per day for 17 days and finally 300 mg. per day. It was not until the latter dosage had been instituted for several days that the serum ascorbic acid level and the urinary excretion of the vitamin rose to normal values (figure 2).

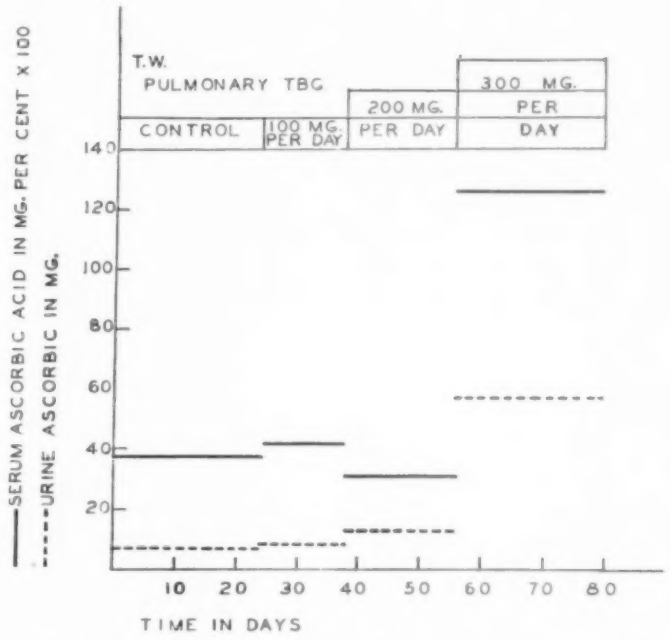

FIG. 2. The effect of oral administration of ascorbic acid on the serum values and urinary excretion of this substance in a patient with pulmonary tuberculosis.

DISCUSSION

The above experiment indicates that this patient who had active tuberculosis required more than 200 mg. of ascorbic acid per day to keep his plasma level and urinary secretion of the vitamin at normal levels. This may be compared to the figures of van Eckelen [23] and of Heinemann [24] who found that the daily requirements of a normal adult weighing 70 kg. are about 60 mg.

Summary

The serum ascorbic acid has been estimated in a group of normal individuals, in patients with vitamin C deficiency, and in patients with infectious diseases.

The serum ascorbic acid levels in patients with infections are usually well below the values seen in normal individuals and often reach figures encountered in manifest clinical scurvy.

The amount of vitamin C in the diet necessary to bring the serum level and the urinary output to normal values in the presence of infection is far greater than the normal requirements.

The effect of rheumatic fever on the vitamin C metabolism appears to be the same as that of other infectious diseases.

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THE EFFECTS OF LARGE DOSES OF BENZEDRINE SULPHATE ON THE ALBINO RAT: FUNCTIONAL AND TISSUE CHANGES *

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OF the synthetic preparations of the epinephrine group, benzedrine (phenylisopropylamine) is in some respects more efficient than epinephrine and ephedrine, and also has additional therapeutic effects. As a sympathetic stimulant it produces mydriasis and piloerection (Alles [1]; Prinzmetal and Bloomberg [2]; Myerson, Loman and Dameshek [3]). It raises both blood and spinal fluid pressure, the rise being maintained for a longer period than after injection of the other two drugs (Alles [1]; Piness, Miller and Alles [4]; Hartung and Munch [5]; Tainter [6]; Myerson, Loman and Dameshek [3]). Like these drugs, it increases the number of erythrocytes and leukocytes in the blood, and to a lesser extent the hemoglobin and the corpuscular volume (Myerson, Loman and Dameshek [3]). Applied to the mucous membranes of the nose, Eustachian tube or middle ear, benzedrine has a marked decongesting effect (Bertolet [6]; Bryne [6]; Scarano [6]; Wood [6]). In addition, it has been found to diminish the sense of fatigue, to prevent sleep, and to be of therapeutic value in the narcolepsies and allied conditions (Prinzmetal and Bloomberg [2]). Finally, it has been shown to lessen or abolish spastic manifestations of the gastrointestinal tract within a few minutes (Myerson and Ritvo [7]).

Most of these studies have been on clinical material; those on animals were not continued over long periods and did not include postmortem studies which might throw light on possible toxic effects.

It seemed desirable, therefore, to undertake studies on rats which would disclose signs of toxicity when benzedrine in hypertherapeutic amounts was given over long periods, and also establish the postmortem changes following lethal doses.

METHODS

For these experiments, 171 albino rats, weighing from 50 to 385 grams, were used; 145 rats were injected subcutaneously with benzedrine sulphate which had been dissolved in saline solution and sterilized by heat. The amount of benzedrine given by single injections varied from 1 to 500 mg. per kilo of rat weight. Injections, with but few exceptions, were made on

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the first, fourth and sixth days and thereafter daily—six days a week—in one group for one and one-half weeks, in another for three weeks, in another for six weeks. Surviving rats were sacrificed and immediately autopsied 24 hours after the last injection, except in the case of one lot that was used to study the effect of increasing doses.

Of the remaining 26 rats, which served as controls, nine were injected with 0.5 to 2.0 c.c. of saline, while 17 received no injections.

To estimate functional changes, we observed the general behavior of the rats, the weight curve, the blood picture, and the blood urea. The blood picture was determined from a drop of blood from an incision in the dorsal surface of the tail. To avoid a possible anemia from loss of blood, we made only two to four counts on each rat of the number of the red and white cells and differential counts, according to standard routine. The blood urea was determined from blood collected after the animals had been decapitated. For these determinations we are indebted to Dr. W. G. Karr, of this University, who used the method of Folin and Wu.

For the morphological study, pieces of liver, kidneys, adrenals, heart, aorta, intestine, spleen, lungs and brain were fixed in alcohol, formalin and Zenker-formalin. The sections were stained with hematoxylin-eosin, Azur II-eosin, Best's carmine and Sudan III. In most instances stains for calcium and iron were also made.

Results

1. *Lethal Dose.* The lethal dose was determined first, since it should also show toxic effects, if there were any, especially with high sublethal doses. The results of these studies are given in table 1. Since heavier (older) rats

Table I

Lethal Dose of Benzedrine in Different Weight Groups

Dosage mg./1000 grams	Weight 50 to 95 grams				Weight 100 to 195 grams				Weight 210 to 385 grams			
	No. of rats	Average weight (grams)	Number dead after first injection	fifth injection	No. of rats	Average weight (grams)	Number dead after first injection	fifth injection	No. of rats	Average weight (grams)	Number dead after first injection	fifth injection
20	3	88	0	0	13	140	0	1†(8)				
25					4	133	0	1*(25)	4	268	0	0
30	2	90	0	0	7	148	2‡(29)	2‡(29)	5	316	2(40)	3(60)
35	1	90	0	0	6	136	1†(17)	1†(17)	1	320	0	1(100)
40	4	80	0	0	9	150	1(11)	2(22)	2	243	2(100)	2(100)
50					11	135	5(45)	7(64)				
60	1	80	0	0	7	161	4(57)	5(71)				
80	3	77	0	0	5	119	4(80)	4(80)				
100	6	76	1†(17)	2†(33)	5	117	5(100)	5(100)				
150	4	81	1(25)	1(25)	3	130	3(100)	3(100)				
200	4	85	2(50)	4(100)	3	133	2(67)	2(67)				
300	2	75	2(100)	2(100)								
400	2	88	2(100)	2(100)								

Figures in parentheses = percentage dead.

* In this rat death was due to paratyphoid.

† In these rats the cause of death could not be ascertained, because they were found to be eaten up or completely autolyzed.

‡ In one of these rats death was due to pneumonia, whereas the other apparently died from benzedrine.

regularly died from much smaller doses per kilo than lighter (younger) ones, the results are presented in three groups: the first comprising animals weighing 50 to 95 grams; the second, 100 to 195 grams; and the third, 210 to 385 grams.

If we consider as the minimum lethal dose one which kills half or more of the animals injected, we find that for rats weighing 50 to 95 grams, this dose is about 200 mg. per kilo; for rats weighing 100 to 195 grams, 50 to 60 per kilo; and for rats weighing 210 to 385 grams, 30 to 40 per kilo. Of the 10 rats which died with smaller doses, six could be examined histologically. Of these, one showed a heavy paratyphoid infection, and one an extensive purulent pneumonia, whereas the other four apparently died from benzedrine.

In general, the rats died the more quickly the larger the dose given. This holds true for all three weight groups.

The question why seven rats (excluding those that had complicating infections) died only after several injections cannot be answered with certainty. But since four of them received the second injection three days after the first only, and the third two days after the second, and since these rats died only after they had received two to three *daily* injections, it might very well be that the drug was not eliminated completely during the 24 hours between the injections, or that they had not recovered completely before they were again injected. As far as we can learn, there is as yet no knowledge of the method and rate of elimination of the drug or of its destruction within the body. That its action lasted more than eight hours can be deduced from the fact that treated rats ate less the next night (12 to 24 hours after the injection) and that rats which received large doses frequently were found to be still excited 24 hours after the injection.

As to tolerance, we have definite evidence that it was increased by repeated injections, in animals which survived the first four or five. If we injected 20 to 150 mg. per kilo for four to 21 days and increased doses thereafter until the animals died, we found (table 2) that in most animals the dose had to be increased to 300 to 500 mg. per kilo to have a lethal effect.

In regard to the minimum lethal dose, our figures are considerably higher than the 25 mg. per kilo reported by Hartung and Munch [5] for benzedrine hydrochloride. While there should be little difference in the action of equal doses of the two salts, 100 mg. of the hydrochloride being equivalent to 107 mg. of the sulphate, the discrepancy may be explained by the different weights (ages) of the animals used. In our series only the third group consisted of adult or almost adult rats, while those of Hartung and Munch may all have been fully adult or even aged.

2. *General Behavior.* As soon as 15 minutes after the first injection the rats began to run around excessively, to gnaw at the iron wires of their cages, and, when a dish of water was in the cage, to splash in it. The pupils were very wide and with larger doses did not react to light. The degree

and the course of this excitement varied with the dose of benzedrine. Rats receiving 1 to 5 mg. per kilo of weight were not at all or moderately excited after two to three hours, almost calm after four hours, and quite calm after six to seven hours; rats receiving 5 to 20 mg. were much excited after two and a half hours, moderately excited after four hours, and calm to moderately excited after six to seven hours; rats receiving 20 to 80 mg. were very much excited after two and a half to three hours and after four hours; and moderately to much excited after six to seven hours. Rats which received 30 mg. or more showed very queer movements; they ran backwards or in circles, even had difficulty in walking, often sat up on their hind legs, pawing the air and falling over backward. Many rats developed diarrhea.

TABLE II

Lethal Dose of Benzedrine if Applied Daily in Increasing Doses (27 Rats)

No. of rat	Weight (grams)	Benzedrine mg./1000 grams	Total mg. per kilo given	Total no. of doses	Found dead hrs. after last injection
18/1	75	100(5), 150(1), 200(1), 300(1)	1150	8	1
18/2	80	100(5), 150(1), 200(1), 300(1), 400(1)	1550	9	4½
18/3	80	150(5), 200(1), 300(1), 400(1)	1650	8	1½
37	85	150(4), 200(1), 300(1)	1100	6	1
21	90	30(5), 80(1), 100(1), 150(1), 200(1), 300(1)	980	10	3
22	95	40(5), 80(1), 100(1), 150(1), 200(1), 300(1), 400(1)	1430	11	½
8/5	110	20(21), 80(1), 100(1)	600	23	6
20/6	110	35(4), 40(1), 50(1), 60(1), 80(1), 100(1), 150(1), 200(1), 300(1)	1120	12	1
7/7	115	20(21), 60(1), 80(1), 100(1)	660	24	3½
20/9	115	35(4), 40(1), 50(1), 60(1), 80(1), 100(1), 150(1), 200(1), 300(1), 400(1), 500(1)	1820	14	½
20/8	115	40(4), 50(1), 60(1), 80(1), 100(1), 150(1), 200(1), 300(1), 400(1)	1500	12	2
8/7	120	20(21), 80(1), 100(1)	600	23	4
8/3	120	20(21), 100(1)	520	22	1
20/7	125	40(4), 50(1), 60(1), 80(1), 100(1), 150(1), 200(1), 300(1), 400(1)	1500	12	2
24	155	30(5), 100(2), 150(1), 200(1)	600	9	5
17/5	165	30(5), 40(1), 50(1), 60(1), 80(1), 100(1)	480	10	3–47
17/6	165	30(5), 40(1), 50(1), 60(1), 80(1)	380	9	7
20/5	170	35(4), 40(1)	180	5	3½
20/1	185	35(4), 40(1), 50(1), 60(1), 80(1), 100(1), 150(1), 200(1), 300(1), 400(1)	1520	13	½
20/3	190	40(4), 50(1), 60(1), 80(1), 100(1), 150(1), 200(1), 300(1), 400(1), 500(1)	2000	13	1½
7/6	195	20(21), 60(1), 80(1), 100(1), 150(1), 200(1), 300(1), 400(1)	1710	28	½
16/5	210	25(4), 30(1), 35(1), 40(1), 60(1), 80(1), 100(1), 150(1), 200(1), 300(1), 400(1)	1495	14	2
16/6	210	25(4), 30(1), 35(1), 40(1), 60(1), 80(1), 100(1), 150(1)	595	11	2
21/3	290	30(4), 35(1), 40(1), 50(1), 60(1), 80(1), 100(1), 150(1), 200(1), 300(1)	1135	13	2
21/2	310	25(4), 30(1), 35(1), 40(1), 50(1), 60(1), 80(2), 150(1), 200(1), 300(1), 400(1)	1525	15	2½
16/3	320	30(4), 35(1), 40(1), 50(1), 60(1), 80(1), 100(1), 150(1), 200(1), 300(1)	1135	13	6
21/4	340	25(4), 30(1), 35(1), 40(1), 50(1), 60(1), 80(1), 100(1), 150(1)	645	12	6

Figures in parentheses = number of injections given at each dosage level.

After repeated injections similar observations were made. After the third or fourth injection, it was also noted that the rats which received 30 mg. or more fought a great deal. In two rats receiving 10 and 30 mg. per day a very unusual phenomenon was observed: Three hours after the second injection they were found to gnaw their own thoracic skin.

After injections had been continued for more than one to two weeks, rats did not react as strongly as they did after the first injections: They were less excited; and for shorter periods.

A rat about to die from benzedrine lay down and " faded away." Al-

though the death of practically all the rats was observed, nothing approaching tremors or convulsions, as reported by Alles [1] for guinea-pigs, was observed at any time.

3. *Weight.* Of the 55 rats the weights of which have been followed, 30 were discarded when found to be sick from spontaneous diseases. Of the 25 remaining rats, 16 have been followed for three to six weeks. The weight curves of these rats are given in figures 1 to 3, together with normal weight curves, as given by Donaldson and Ferry.[8] Comparison shows that at first most rats stopped growing for three to four weeks, after which most of those receiving less than 20 mg. per day grew again, while those receiving higher doses failed to do so. It can also be seen that younger rats (figure 1) did better than older ones (figure 2).

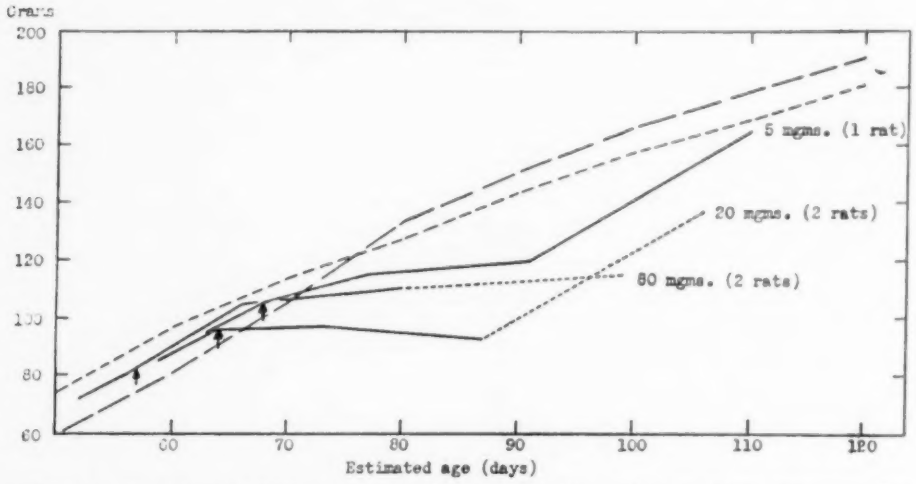

FIG. 1. Transient inhibition of growth by daily injections of benzedrine. ——— Experimental rats (male, weight group 50 to 95 grams); the dotted continuation gives the curve of the one rat that survived. — — — Normal weight curve based on data of Donaldson, Dunn and Watson. - - - - - Normal weight curve based on data of Ferry. An arrow indicates when benzedrine dosage was started.

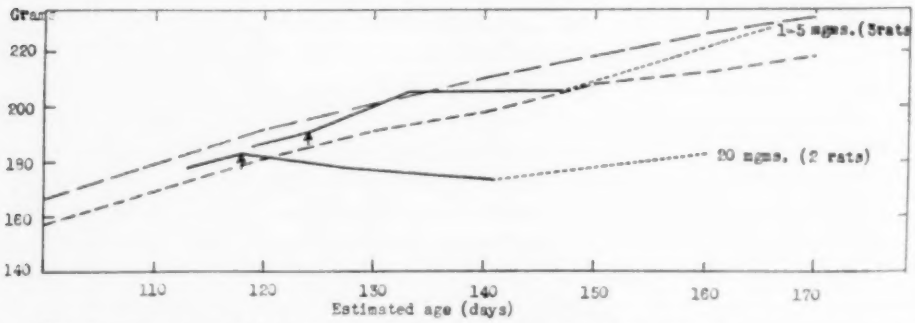

FIG. 2. Transient inhibition of growth by daily injections of benzedrine. ——— experimental rats (male, weight group 150 to 205 gm.); — — —, - - - - -, and arrow, as in figure 1.

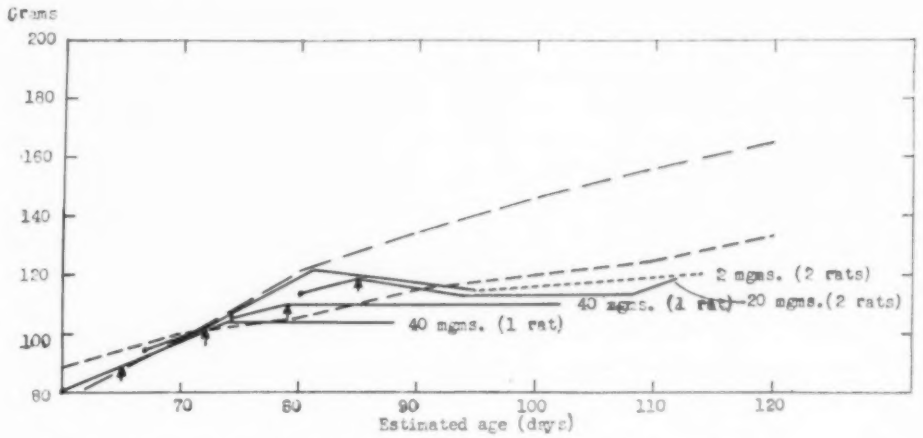

FIG. 3. Transient inhibition of growth by daily injections of benzedrine. ——— experimental rats (female, weight groups 50 to 95 and 100 to 130 gm.); —— ——, – – – –, and arrow, as in figure 1.

Weight changes and food intake of the remaining nine rats (four treated with benzedrine, and five controls) are given in table 3. They correspond to the previous figures. In addition, they show that the daily food intake, as measured by weighing the amount of food (Purina Dog Chow) given in the morning and left on the next morning, was conspicuously lowered in

TABLE III

Changes of Weight and Food Intake During Nine Days of Treatment

No. of rats	Original weight (grams)	Treatment	Average weight increase (per cent)	Average daily food intake (grams)
		Control Group		
2	75–100	None	+51	17.5
2	80–100	1 c.c. saline	+58	
1	155	1 c.c. saline	+16	
		Benzedrine		
2	85–100	50–100 mg.	+16	13.7
2	155–165	25 mg.	+ 3	

the treated animals as compared with the controls. This finding indicates that decreased food intake is a factor in the inhibition of growth.

4. *Red and White Blood Cells.* The changes in the number of erythrocytes and leukocytes in the blood have been followed in 36 treated and six control rats. In all instances the determinations were made 24 hours after the last injection. As 21 of the treated animals and four of the controls had to be excluded on account of the presence of spontaneous disease at autopsy, the counts on 15 treated and two control rats only were available.

The changes in the number of erythrocytes in our treated rats are presented in figure 4. For comparison, the normal increase in the number of erythrocytes (which in our rats amounted to 0.22 millions of erythrocytes per 10 grams of weight increase) has been given. We found that, with the exception of two rats which received 1 mg. benzedrine daily, all our rats responded with an erythrocytosis. Whereas in the rats receiving 2 to 5 mg. of benzedrine daily this increase amounted to 40 per cent on the sixteenth day; in those receiving 20 mg., it amounted to about 50 per cent after 16 to 23 days, and in those receiving 40 to 80 mg. to 55 per cent, after 43 days, i.e., on the last day of this experiment.

The individual leukocyte counts were not as uniform as the erythrocyte counts, and there were no distinct differences in the animals treated with different doses. On the average, at first both granulocytes and lymphocytes

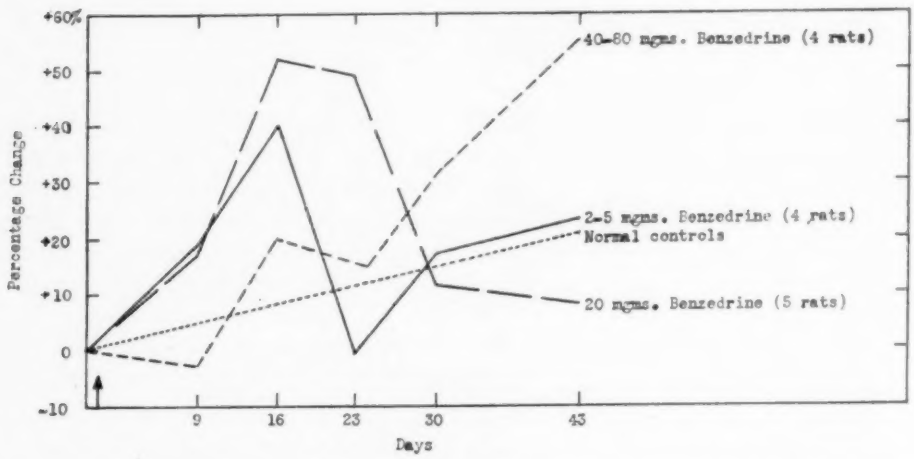

FIG. 4. The percentage changes in the number of erythrocytes after 2 to 5; 20; and 40 to 80 mg. of benzedrine daily. An arrow shows when benzedrine dosage was started.

rose considerably. After 16 days there was a marked preponderance of granulocytes, and after 23 days of lymphocytes. After 30 days, however, both granulocytes and lymphocytes had returned to normal in spite of the daily dosage being continued (figure 5).

These findings correspond in general to those of Myerson, Loman and Dameshek in men, as well as to those which have been obtained with epinephrine and ephedrine in a variety of animals. As to the mechanism producing these changes no new information was obtained. It may be mentioned that in a few animals tested the icterus index was normal.

5. *Blood Urea.* The blood urea has been determined in 33 treated and five control rats, 28 to 29 hours after the last injection. In all the rats receiving 1 to 20 mg. of benzedrine daily for three or six weeks, or 30 to 200 mg. for one and a half weeks (with the exception of three rats which had

an extensive spontaneous disease) the blood urea was found to be within normal limits: 17 to 26 mg. per cent (average 23 mg. per cent), as compared with 20 to 24 mg. per cent (average 23 mg. per cent) in our controls. In the four rats which received 40 to 80 mg. daily for three or six weeks it was found to amount to 34, 50, 52 and 70 $\pm$ mg. per cent. Since two of these rats showed no spontaneous disease whatsoever, and another had one tapeworm only, it may be assumed that in these animals the rise in blood urea was due to the injections.

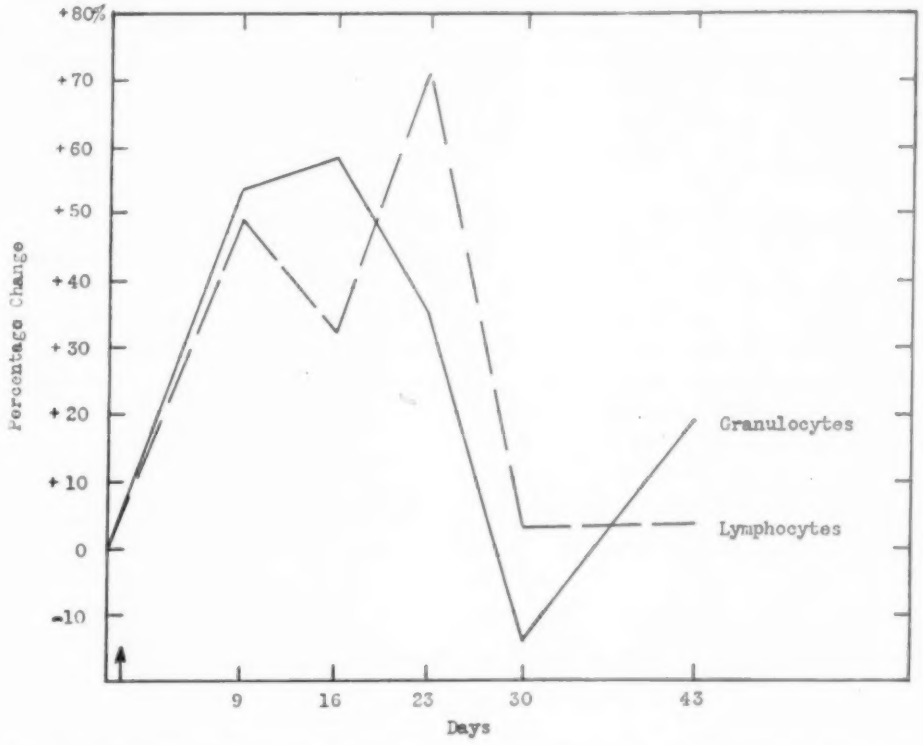

FIG. 5. The percentage changes in the number of granulocytes and lymphocytes after 1 to 80 mg. of benzedrine daily. An arrow indicates when benzedrine dosage was begun.

6. *Gross Pathology.* In the animals which were killed by the benzedrine, various lesions were found. Frequent changes were: Marked and sharply delimited constrictions of the small intestine; air and fluid in stomach and intestine; congestion of the liver; either contraction or congestion of the spleen, and subpleural hemorrhages in the lungs. As the changes in the amount of blood in spleen and liver appear to be of special interest, we have tried to analyze them (table 4). Correlating these changes with the time which elapsed between injection and death, we find that the congestion of the liver was most marked in the animals which died after two hours,

TABLE IV

Amount of Blood in Liver and Spleen in Rats Which Died from Benzedrine, as Compared with the Time the Rats Survived

Died hrs. after last injection	No. of rats	Average dose of benzedrine (mg.)	Average weight (grams)	No. of rats showing different amounts of blood in:					
				Liver			Spleen		
				Normal	Slight incr.	Great incr.	Decr.	Normal	Incr.
—	10	0	112.5	10	0	0	1	9	0
½–1	4	300	124	1	2	1	2	0	2
1½–2	7	179	121	0	0	7	4	2	1
3–5	13	167	130	0	7	6	6	1	6
6–24	3	57	155	1	1	1	1	1	1

less marked after three to five hours, and less marked still after six to 24 hours; whereas the changes in the spleen showed no relationship to the time of death after injection. However, comparison with the dosage of benzedrine (table 5) shows that most of the animals which received 30 to 100 mg. had *congested* spleens, and those which received 150 to 400 mg. *contracted* spleens, whereas the livers showed no relationship. From these findings we may conclude that the contraction of the spleen was due to the action

TABLE V

Amount of Blood in Liver and Spleen (Percentage Incidence) in Rats Which Died from Benzedrine, as Compared with the Dose Given

Dose of benzedrine (mg.)	No. of rats	Average weight (grams)	Died hrs. after last injection (average)	Amount of Blood in:					
				Spleen			Liver		
				Decr.	Normal	Incr.	Normal	Slight incr.	Great incr.
0	10	112.5	—	10*	90	0	100	0	0
30–100	12	147.5	4.4–5.6	25	17	58	8	42	50
150–400	15	115	2.5	67	13	20	7	27	66

* Percentage of rats.

of benzedrine, whereas the congestion of the liver and spleen was merely a sign of the circulatory insufficiency that existed just before death. The fact that the spleens of the rats which received smaller doses of benzedrine were congested in most cases may be explained by the assumption that in these animals the effect of circulatory failure was greater than that of the benzedrine, whereas in the animals with larger doses the effect of the drug

predominated. As the surviving animals which were killed 24 hours after the last injection showed no lesions attributable to the treatment, they are omitted here.

7. Histology. A. Necroses. With the exception of 11 rats which were eaten up or in an advanced state of autolysis, all rats were carefully examined histologically. In no instance, not even in animals which for six weeks received 40 to 80 mg. of benzedrine daily, were we able to find areas of degeneration, necroses or calcification in the myocardium, in the arteries or in the muscular coat of the intestine, as described in chronic adrenalism (Petri[9]). Nor did we find any "parenchymatous degeneration" of the kidneys as described by Chen[10] after administration of ephedrine. Many slides, to be sure, showed vacuolization of the tubular epithelial cells when fixed in alcohol and stained with hematoxylin-eosin, or a fibrinoid granulation of these cells when fixed in Zenker-formalin and stained with Azur II. Although this observation is of interest pathologically and, as far as we know, has not been previously reported, it is not relevant to the present study, as it was obviously dependent upon spontaneous diseases of the rats, especially upon paratyphoid and purulent infections (see table 6).

TABLE VI

Tubular Degeneration of Kidneys as Compared with Benzedrine Injections and Spontaneous Disease

	No. of animals	Tubular degeneration			
		0	+	++	+++
Controls (healthy)	15	9	2	3	1
Benzedrine (healthy)					
1– 25 mg.	13	11	1	0	1
30– 50 gm.	15	13	1	1	0
60–100 mg.	11	11	0	0	0
150–400 mg.	13	13	0	0	0
Paratyphoid					
Mild	12	5	6	1	0
Medium	9	0	2	6	1
Heavy	10	0	1	2	7
Purulent bronchopneumonia, appendicitis, middle ear infection, etc.	7	3	1	2	1

The only changes which could be connected with the benzedrine injections were necroses in liver, spleen and kidneys, and changes in the sugar and fat depots. Necroses in liver, spleen and kidneys were found only in rats which died from benzedrine. Rats which survived the injections never showed any necroses or scars when killed later. If we compare the occurrence of necroses with the dosage of benzedrine (table 7), we find that only those rats which died from 30 to 100 mg. of benzedrine per kilo exhibited necroses, whereas those which received higher doses did not. A similar

TABLE VII

Liver Necroses as Compared with the Dose of Benzedrine Given (Single Doses)

Dose of benzedrine (mg.)	No. of rats	Liver necroses			
		None	Slight	Medium	Extensive
30– 40	9	1	1	2	5
50– 60	11	2	3	4	2
80–100	6	2	2	1	1
150–200	5	5	0	0	0
200–400	6	6	0	0	0

result was obtained when the animals were treated with increasing doses (table 8). As to the cause of this phenomenon we have no explanation at present.

TABLE VIII

Liver Necroses as Compared with the Dose of Benzedrine Given (Increasing Doses)

Highest dose of benzedrine given (mg.)	No. of rats	Liver necroses			
		None	Slight	Medium	Extensive
40– 80	2	0	0	1	1
100–150	7	1	3	2	1
200–400	18	18	0	0	0

B. Carbohydrate and Fat Changes. Changes in the sugar and fat depots on the other hand were found in both groups of rats. If rats, after one and a half weeks of treatment, were killed by ether one day after the last injection, and if they had no spontaneous diseases, the glycogen content of the liver as well as of the para-aortal, para-renal, para-adrenal and mesenteric fat tissue, as seen by Best's carmine stain, was found to be increased in those rats receiving more than 25 mg.; whereas the fat content of these organs was found in Sudan III stained slides to be decreased (table 9). Similar results were obtained by a chemical analysis for which we are indebted to Dr. Evans of the Cox Institute (table 10). Since fat tissue could not be obtained in an amount large enough to permit such an analysis, this was not studied. Instead, the heart glycogen was determined; this, however, appeared to be within the normal limits (table 10).

In the rats killed after three or six weeks of treatment the glycogen could not be determined correctly, because the time between decapitation and fixation of tissues was long enough to have permitted loss of glycogen. The fat, however, could be estimated, since its values do not change as quickly after death as those of glycogen. The results of this estimation are in accord with the findings after one and one-half weeks (table 11).

TABLE IX

Changes in Glycogen and Fat after One and a Half Weeks of Treatment with Benzedrine

Glycogen

Treatment	No. of rats	Liver				Fat tissue			
		None	Slight amt.	Mod. amt.	Great amt.	None	Slight amt.	Mod. amt.	Great amt.
Controls									
None	15	1	3	7	4	12	2	1	0
Saline	3	0	1	2	0	3	0	0	0
Benzedrine mg.									
2	1	0	1	0	0	1	0	0	0
25	3	0	0	3	0	1	2	0	0
30–50	9	0	0	3	6	1	3	2	3
60–100	6	0	0	2	3	1	1	2	2
150–200	2	0	0	0	2	1	1	0	0

Fat

Contols									
None	13	1	2	4	6	0	0	2	11
Saline	—	—	—	—	—	—	—	—	—
Benzedrine mg.									
2	1	0	0	1	0	0	0	0	1
25	1	0	0	1	0	0	0	0	1
30–50	8	4	4	0	0	0	0	4	4
60–100	5	4	1	0	0	0	0	4	1
150–200	2	2	0	0	0	0	0	2	0

TABLE X

Changes in Glycogen and Fat after One and a Half Weeks of Treatment with Benzedrine (Chemical Analysis)

Treatment	Rat No.	Weight gm.	Glycogen per cent		Fat per cent liver
			Liver	Heart	
Average (6 Controls, Dr. Evans)	—	—	2.08	0.414	—
Our controls					
None	15/2	125	1.37	0.424	3.87
"	15/4	140	1.60	0.437	—
Saline	15/1	130	1.47	0.386	3.35
"	15/3	155	2.48	0.399	3.85
"	15/5	180	2.20	0.382	—
Average		146	1.87	0.403	3.69
Benzedrine					
100 mg.	14/1	95	2.84	0.258	2.65
50 "	14/4	120	2.63	0.325	3.02
25 "	14/5	160	2.19	0.495	2.95
25 "	14/6	170	3.02	0.700	—
Average		136	2.67	0.445	2.87

TABLE XI

Changes in Fat after Three and Six Weeks of Treatment with Benzedrine

Treatment	No. of rats	Liver				Fat tissue			
		None	Slight amt.	Mod. amt.	Great amt.	None	Slight amt.	Mod. amt.	Great amt.
Controls									
None	13	1	2	4	6	0	0	2	11
Saline	2	0	0	1	1	0	0	0	2
Benzedrine mg.									
1–5	6	1	1	2	2	0	0	3	3
10–20	5	1	3	1	0	0	0	2	3
40–80	3	3	0	0	0	0	0	3	0

In addition, they seem to indicate, that after three or six weeks' treatment the decrease in fat is more pronounced still, and that it is apparent already in animals which received less than 25 mg. of benzedrine per day.

In the rats dying after one or two injections of benzedrine, no glycogen was found in liver or fat tissue; if the animals died after six to 11 increasing doses, however, invariably an increase in glycogen was noted. The fat content of the liver was not changed in the first group, whereas in the latter group we found no fat whatsoever in the liver and a markedly decreased amount in the fat tissue.

Concerning the significance of these findings, it may be mentioned that after epinephrine the liver glycogen is also first decreased and then increased (Cori [11]). As to the mechanism involved in these changes we have no new suggestions to offer.

COMMENT

The question whether benzedrine if given in large doses has toxic effects or not is difficult to answer. We have found that in experimental doses (which it should be remembered are from five to several hundred times the human therapeutic dose) it may cause excitement, diarrhea, mydriasis, transient inhibition of weight increase in young rats, erythrocytosis, leukocytosis and changes in the glycogen-fat content of liver and fat tissue. Most of these changes were temporary, some for hours only (excitement, mydriasis, diarrhea), some for weeks (erythrocytosis, leukocytosis, inhibition of weight increase). The changes in the glycogen-fat content of liver and fat tissue appeared to be permanent during the time that benzedrine was given.

It was also found that the lethal dose was proportionately higher for small (young) rats than for large (old) ones, and that large doses caused more marked and longer lasting changes in both large and small rats than did small ones. For instance, most of the animals receiving 25 mg. of benzedrine or more were much more affected than those receiving smaller doses; they were the only ones which showed: (1) queer body movements

after each injection; (2) a definite increase in glycogen and a definite decrease in fat in liver and fat tissue; (3) a persisting failure to increase in weight, and (4) a persisting increase in the number of erythrocytes in the blood.

Whether or not these changes should be looked upon as toxic, appears to be a matter of definition; for if we should call those doses toxic which merely produce transient, undesirable functional variations, then such relatively small doses as 2 to 5 mg. of benzedrine per kilo would be regarded as toxic. But if we regard as toxic only those doses which produce actual lesions, i.e., pathologic tissue changes, then the toxic dose appears to be practically the same as the lethal dose. This in rats under 100 gm. weight was found to be about 200 mg. per kilo; in rats of 100 to 195 gm., 50 to 60 mg.; and in rats over 200 gm., 30 to 35 mg.

The evidence is clear cut that smaller (younger) rats are more resistant to equivalent doses of benzedrine than larger ones. The reason for this, however, is quite obscure to us, especially as we know of no studies that demonstrate the fate of benzedrine in the body. Whether the younger animal can break down or excrete the substance more rapidly or completely than the older, or whether the younger tissues are intrinsically more resistant to the drug, or the circulation more efficient in the young, are questions that remain unanswered.

Summary

The functional and structural changes produced by the subcutaneous injection of benzedrine sulphate into rats were studied in widely varying doses over varying periods. One hundred and seventy-one albino rats, weighing from 50 to 385 gm., were used. One hundred and forty-five were injected subcutaneously with doses of 1 to 500 mg. per kilo from 1½ to 6 weeks.

The minimum lethal dose decreased with the weight (age) of the rats. In animals of 50 to 95 gm. it amounted to 200 mg.; in rats of 100 to 195 gm., to 50 to 60 mg.; in rats of 210 to 385 gm., to 30 to 35 gm. per kilo. After repeated injections an increased tolerance was noted.

If 2 to 5 mg. or more were given, the rats showed excitement, diarrhea, mydriasis, transient inhibition of weight increase, erythrocytosis, leukocytosis and so on. With 25 mg. and more they showed an increase in glycogen and a decrease in fat in liver and fat tissue.

In rats which died from the drug, frequent changes were: Constrictions of the small intestines; congestion of the liver; either marked constriction or congestion of the spleen and subpleural hemorrhages in the lungs. Rats which died from 30 to 100 mg. of benzedrine showed necroses in liver, spleen and kidneys, whereas those which died from higher doses did not. Lesions in the myocardium, arterial or intestinal walls, such as observed in chronic adrenalinism, were not found. Rats killed after recovery from nonlethal doses showed no detectable lesions.

Conclusions

The minimum lethal dose of benzedrine sulphate given subcutaneously to rats is from a hundred to a thousand times per kilo the usual therapeutic dose given man orally.

The greatest non-toxic dose, i.e., that which fails to produce transient variations, appears to be from 2 to 5 mg. per kilo, in other words about 10 to 50 times per kilo the usual human therapeutic dose.

The failure of repeated sublethal doses to produce detectable lesions in rats indicates that there should be a considerable margin of safety in the proper therapeutic use of the drug.

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CASE REPORTS

GLOSSOPHARYNGEAL NEURALGIA DUE TO AN IMPACTED WISDOM TOOTH *

By David Riesman, M.D., Sc.D., F.A.C.P., *Philadelphia, Pennsylvania*

In a recent article Hoover and Poppen [1] call renewed attention to tic douloureaux involving the glossopharyngeal nerve. They report two cases of their own and collect a number of others recorded in the literature. The pain is of the same nature as that of tic douloureaux except that it is located at the base of the tongue and in the back of the throat instead of in the face.

Medical treatment is not very effective—it consists chiefly of the inhalations of from 15 to 30 drops of trichlorethylene three or four times a day. Such treatment frequently stops the pain but does not in any sense bring about a cure. In a number of cases, including one of Hoover and Poppen's, surgical treatment has been employed. In their opinion intracranial section of the ninth nerve in the posterior fossa, a formidable operation, is the procedure of choice.

I want to call attention to a cause of glossopharyngeal neuralgia which should it exist renders such an operation entirely unnecessary, nothing more being required than the extraction of an impacted wisdom tooth.

The first case concerns a man about 50 years of age who began to have violent pains in the throat on eating and speaking. He was obliged to lecture frequently and sometimes while lecturing he would be seized with such a spasm of pain that he thought he would become delirious. The pain would not last long but while it lasted the patient had to hold on to something for fear of falling in a faint. The pain was felt in the back of the throat, in the tonsillar region, and at the base of the tongue —never in the teeth. Throat specialists told him he had gout and ordered salicylates and iodides, but the treatment had not the slightest effect. A dentist declared the teeth normal except for an impacted wisdom tooth. Thinking that this tooth might be responsible for the frightful neuralgia, I insisted that the tooth be removed. It was extracted with difficulty by the late Dr. Matthew Cryer, but from that time on the man has been entirely free from pain. The tooth itself was healthy.

The second patient was a man of 48 years who while in good health was suddenly seized with agonizing pain in the throat which unlike the pain in the first case was not paroxysmal but was more or less constant. For 10 days he had hardly had any sleep despite a variety of strong sedatives. A dentist had declared his teeth to be normal. The case was so similar to the other that I suspected an impacted wisdom tooth. The roentgen-ray films showed such a tooth. It was extracted and the pain disappeared immediately and never returned. Neither of the two patients had any toothache or connected the pain with his teeth.

On the basis of these two impressive experiences I would advise search for an impacted wisdom tooth in cases of glossopharyngeal neuralgia and if one is

* Received for publication January 22, 1937.

found, that it be extracted, regardless of a dentist's opinion to the contrary, before resorting to more radical measures.

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MAJOR PSYCHOSIS IN UNDULANT FEVER*

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Mental symptoms have frequently been observed during the course of undulant fever. In a study of 154 cases, we have encountered only one major psychosis. We found no reference to this condition as a complication of undulant fever in the American literature. Nouvilas [1] reported four cases from the Asylum of Navarre; Roger [2] collected 15 cases from the literature and reported three of his own. In a series of 200 cases, Cantaloube [3] reported delirium in 12 and mental confusion in ten.

Case Report

T. H., a white male business college student, aged 23, was admitted to the hospital January 8, 1936, in a state of violent catatonic excitement.

His illness had begun December 20, 1935, with a sore throat, chilly sensations, fever of 102° F., sweating, stiffness and soreness in the back of the neck. Two weeks later, as he continued to have fever from 100° F. to 101° F. and drenching sweats, he was sent to a hospital where it was found that his blood serum agglutinated *Br. abortus* in a dilution of 1:640. It was learned that he had been a habitual drinker of raw milk. His condition was diagnosed as undulant fever. After a short period of observation he was sent home. January 6, he was despondent, irritable, and, at times, mildly delirious. On this date he was given 0.25 c.c. of *Br. abortus* vaccine intramuscularly. This was followed in a few hours by increased fever, chills, and a more severe delirium. The reaction subsided promptly but recurred the next day following the administration of 0.5 c.c. of the vaccine. He was mildly confused when seen in consultation January 8. It was decided that he should be sent to the hospital for observation. When the ambulance came for him, he became very excited, negativistic and violent.

The family history was entirely negative for mental disturbance.

He had never had a severe illness. He was intelligent and had never shown any psychopathic tendency.

Examination: He was six feet one inch tall and weighed 190 pounds. His axillary temperature was 103° F. and his pulse rate was 120 per minute. Detailed physical examination was impossible on admission because of his violent activity but after large doses of sedatives, he became quiet enough to permit completion of the examination which revealed nothing but a moderate pharyngitis and a dry swollen tongue.

Laboratory examination: Hemoglobin 84 per cent (Sahli); red blood cells 5,700,000; white blood cells 8,150 with 63 per cent neutrophiles, 34 per cent lymphocytes, and 3 per cent eosinophiles. The serum agglutinated *Br. abortus* in a dilution

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of 1:1280. Blood Wassermann and Kahn tests were negative. Urine: Specific gravity 1.009; albumin, negative; sugar, negative; microscopic examination, no cells or casts.

He was very ill; during the first week his pulse ranged from 120 to 150 per minute and his rectal temperature from 104° to 105.8° F. He perspired so profusely that he became dehydrated in spite of an increased oral intake and parenteral administration of fluids. The latter part of the first week he developed a productive cough with râles in the right hilus region and base. These signs disappeared in a few days. While the fever was at its height a mild intention tremor of the hands was present. The temperature reached its peak January 14, after which it fell gradually and by the end of the second week it was only 99.6° to 100° F. There were no abnormal physical findings at this time. No specific therapy was attempted after admission to the hospital.

A lumbar puncture was made January 11, with the following findings: Clear fluid; 18 cm. of water pressure; no block; cell count 1; no increase in globulin; Wassermann negative and no decolorization of gold solutions. Blood cultured the same day was negative a week later. The intradermal test with *Br. abortus* vaccine applied the first week was strongly positive. At the end of the second week the agglutination titer was still 1:1280.

During the first two weeks, his mental state varied from catatonic excitement to stupor. He had to be restrained constantly. In the excited periods, he was violently hyperactive and very noisy. He had both visual and auditory hallucinations to which he responded with obscene accusations and violent threats. There were also absurd transient delusions, usually of a grandiose character. Disorientation was complete for time and space and partial for persons. At times he was rigid, negativistic, and mute. He ate very little but took fluids well. He urinated and defecated in bed. Sedatives had little effect and he slept fitfully, less than five hours in each twenty-four.

After the second week, he was less agitated; seldom rigid or mute but was unchanged otherwise. The insomnia persisted. Early in the fourth week his temperature again increased to 104° F. and was accompanied by increased agitation but the temperature subsided to normal in a few days and the agitation decreased. From this time there was little evidence of toxemia. He ate well and slept fairly well. He had lost more than 40 pounds during his illness. Repeated neurological examinations revealed no evidence of any focal lesion of the brain or spinal cord. Gradually, he became quieter and more tractable and was released from restraints. During the latter part of March, he was allowed to be up in his room when supervised and allowed to go to the bathroom. He continued to be hyperactive and hallucinated. He was very destructive to his clothing and bedding and was frequently nude.

April 9, he was transferred to the State Hospital for the Insane at Osawattomie. There, he was given a therapeutic course of malaria as an empirical procedure. From the early part of May, his mental condition cleared up rapidly and he was dismissed June 15, apparently normal.

Since his return he has been seen frequently. There has been no psychotic tendency. He has regained his normal weight and strength. For a time he continued his studies in the business college and reported normal progress. At present he is working in a packing plant. So far there has been no indication of a return of his undulant fever. September 21, 1936, his agglutination titer was 1:10 complete, 1:40 partial and the opsono-phagocytic reaction marked.

Note: T. H. was contacted May 1, and found to be employed doing stenographic work. There has been no return of his mental symptoms.

Comment. Although the early symptoms of psychosis had preceded the administration of the vaccine, they developed much more rapidly following its

use. The symptoms of general intoxication, likewise, were greatly intensified. We were so impressed by this fact that we considered it unwise to continue the vaccine therapy. The presence of a psychosis, we believed, should be added to the list of contra-indications to the use of vaccine already reported.[4]

The mental symptoms which occur as a result of a toxic or infectious state may develop into typical psychiatric patterns.[5] Such a case was reported by Nouvilas [1] in which the admission diagnosis was schizophrenia, but before the patient left the hospital the diagnosis was revised to acute infectious psychosis. Our case has many features of catatonic schizophrenia, but due to the rapid evolution with complete recovery and the absence of any previous abnormal mental trends, we believe the condition was an acute psychosis due to intoxication from undulant fever. The persistence of the psychosis after the physical signs of intoxication had disappeared is, of course, not unusual in toxic psychosis.

According to Roger [2] the appearance of psychic disturbances in undulant fever has an unfavorable prognostic significance; 10 of the cases which he collected from the literature died.

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PROTAMINE INSULIN AS A CONTRIBUTING FACTOR IN THE DEATH OF A DIABETIC PATIENT WITH CEREBRAL ARTERIOSCLEROSIS *

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Protamine insulin was first used in the United States during 1935 by Root,[1] Joslin [2] and their associates and since then its use has been extended to diabetic patients in other parts of the country under the direction of physicians with considerable experience in the treatment of diabetes mellitus. The number under treatment at present in the United States is probably about 3,000 persons.

By means of its use it has been possible to convert the severe diabetes of a number of patients not easily controlled by the simpler or regular insulin to a relatively mild form due to the prolonged action of the new insulin which often eliminates the sudden and wide excursions of the blood sugar, replacing these with a flatter type of curve. Various other advantages accruing to the patient

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from its uses, such as the reduction in the daily number of injections, the elimination of insulin reactions or the lessening of their severity when hypoglycemia was present, have been observed as compared with the results obtained and effects noted, from the previous use of regular or simpler insulin.

Joslin [2] cautioned against the possible dangers from hypoglycemia, especially if two doses of protamine insulin were used. We have used protamine insulin † since January 1936, in the treatment of over 30 patients and at all times have kept in mind its possible dangers. It is because of a fatality occurring during the treatment of one of our diabetic patients with protamine insulin and because of the possibility that the initial coma, which ended in death, was due to prolonged and extreme hypoglycemia resulting from the long action and cumulative effect of the new insulin, that we present the following case report.

Case Report

The patient, an unmarried white female, a clerk, developed diabetes mellitus at the age of 44, during the latter part of 1931. Since the onset she had lost 71 pounds (32.3 kg.) when first seen in the diabetic clinic on August 26, 1933, had been treated by dietary restriction alone. Subsequent to this a sister developed diabetes following the removal of a goiter and died in coma, and a brother was found by other physicians to have a glycosuria.

At the time of her initial treatment by us she gave no evidence of arteriosclerosis and the only findings of note were evident anemia and a fibroid uterus. Blood pressure averaged 120 systolic and 80 diastolic. The Wassermann and Kahn tests were negative. Following a three week period of unsuccessful dietary treatment she was given standard insulin in increasing doses. On a diet of carbohydrate 90 gm., protein 54 gm. and fat 78 gm., she required 4 doses of insulin averaging 18-12-15-7 units daily. Occasional insulin reactions were experienced. Following a period of hospitalization her diabetes was better controlled on carbohydrate 80 gm., protein 43 gm., and 72 gm. of fat with insulin in doses of 16-8-12-11 units per day. In May 1934, her basal metabolic rate was minus 5 per cent. Her electrocardiogram showed complexes of low amplitude, with T_{1-2} nearly isoelectric. Her weight had increased from 134 pounds (60.9 kg.) to 172 (78.2 kg.). In August 1934, because of the hours of her employment her insulin dosage was 22-14-0-12. From this time until April 1936, her diabetes was never satisfactorily controlled, post-prandial blood sugars varying between 244 and 400 mg. In October 1934, she became comatose at night during an insulin reaction, the incident being preceded by a severe diarrhea.

On April 1, 1936, on a diet of carbohydrate 110 gm., protein 50 gm., and fat 61 gm., she excreted 64 gm. of dextrose during the 24 hours. Protamine insulin was started on April 4, 1936, with immediate improvement in the control of the patient's diabetes. Subsequent treatment with the new insulin changed the diabetes from severe to relatively mild on the basis of ease of control. A synopsis of treatment is given in table 1.

Throughout the treatment of the patient considerable difficulty was experienced by the staff of the diabetic clinic in maintaining proper contact. Due to her reduced financial status she rarely felt able to take sick leave to attend the clinic oftener than every two weeks. Although she was able to come to the hospital laboratory for blood examinations on Sundays and after work, those attending her were rarely able to meet her at these times. Instructions were often given by letter. During the latter part of August 1936, when notes from the patient stated that she was having insulin

† Supplied by Eli Lilly & Co., Inc., Indianapolis, Ind.

TABLE I

Date	Weight Lbs.	Blood Sugar Mg. per 100 c.c.	Time	Insulin		Urine					Remarks
				Regular Units	Protamine Units	24 hr. Dextrose Gm.	a.m.	Noon	6 p.m.	10 p.m.	
3/31/36	165	400	Fasting	22-0-13-5 = 40			3+	—	3+	3+	Insulin protamine started
4/12/36	169			22-0-13-5 = 40		64.0	3+	—	3+	3+	
4/14/36	169			20-0-15-0 = 35	8-0- 6-0 = 14		3+	—	3+	3+	
4/17/36	169	222	3:00 p.m.	15-0-13-0 = 28	8-0- 6-0 = 14		0	—	1+	3+	
4/18/36		250	Fasting	15-0-13-0 = 28	8-0- 6-0 = 14		0	—	3+	1+	
5/12/36	172	166	3:00 p.m.	12-0-14-0 = 26	12-0- 6-0 = 18	26.4	0	—	3+	0	
5/17/36		235	Fasting	10-0-13-0 = 23	14-0- 6-0 = 20		0	—	2+	1	Some evidence of hypoglycemia before lunch
5/31/36	174	100	11:00 a.m.	6-0-14-0 = 20	18-0- 8-0 = 26		0	—	3+	1+	
6/ 7/36	174			6-0-14-0 = 20	18-0- 8-0 = 26	16.4	0	—	3+	1+	
6/ 9/36	174	250	3:00 p.m.	6-0-14-0 = 20	18-0- 8-0 = 26		0	—	2+	1+	
6/16/36	174			6-0-10-0 = 16	22-0-12-0 = 34		0	—	3+	1+	
6/23/36	176	300	3:00 p.m.	0-0-12-0 = 12	30-0-10-0 = 40		0	—	3+	0	
7/12/36	173			0-0-10-0 = 10	32-0- 8-0 = 40	15.6	0	—	2+	0	
7/14/36	173			0-0-10-0 = 10	32-0- 8-0 = 40		0	—	0	0	Reaction at 10 a.m., 4 p.m., and midnight
7/19/36	171	396	Fasting	0-0- 4-0 = 4	36-0- 8-0 = 42		0	—	2+	1+	Insulin protamine with calcium started
7/21/36	171	222	2:00 p.m.	0-0- 0-0 = 0	36-0- 8-0 = 42		0	—	1+	3+	
7/22/36	170	444	Fasting	0-0- 0-0 = 0	40-0- 0-0 = 40		0	—	2+	2+	
7/28/36	170	206	2:30 p.m.	0-0- 5-0 = 5	40-0- 0-0 = 40		0	—	3+	2+	Unconscious at 11:30 p.m.
7/29/36	170	200	5:30 p.m.	0-0- 0-0 = 0	40-0- 0-0 = 40		0	—	1+	0	
8/ 3/36	170	208	Fasting	0-0- 6-0 = 6	40-0- 0-0 = 40		0	—	3+	0	
8/ 4/36	170	200	Fasting	0-0- 0-0 = 0	38-0-12-0 = 50		0	—	2+	0	
8/19/36	170			0-0- 0-0 = 0	38-0-12-0 = 50		0	—	1+	0	Reaction at 6 a.m. Dazed entire day. Unable to work
8/20/36	170			0-0- 0-0 = 0	36-0-10-0 = 46		0	—	0	0	Vertigo at 5:30 p.m. Sweating at midnight
8/21/36	170			0-0- 0-0 = 0	36-0-10-0 = 46		0	—	0	0	Vertigo
8/22/36	170			0-0- 0-0 = 0	30-0-10-0 = 40		0	—	0	0	
8/25/36	170	200	5:00 p.m.	0-0- 0-0 = 0	30-0-10-0 = 40		0	—	0	0	
8/30/36	170	250	11:00 a.m.	0-0- 0-0 = 0	30-0-10-0 = 40		0	—	0	0	Insulin reaction at 2:00 a.m. and chill at 6:00 a.m.
8/31/36 to 9/ 3/36	No record kept by patient Diet C 110 P 50 F 61										

reactions, a number of attempts to communicate by telephone were made without success.

On the afternoon of September 3, 1936, a neighbor noticed that the bottled milk delivered to the patient's home that morning had not been removed from the front porch. Upon investigation the patient was found partially dressed and lying unconscious across her bed. One of us (K. H. M.) was called to see the patient and at 5:30 p.m. found her comatose, with rapid pulse and flaccid extremities. There was no evidence of food having been eaten at any time during the day. Whether or not the morning dose of 30 units of protamine insulin had been taken following the injection of 10 units the night before is not known. One resident in the house reported talking to the patient about 10:00 p.m. on the previous day, at which time she seemed to be quite normal. Other residents of the home stated that they heard her moving about her quarters between 6 and 7 a.m., but no one saw her on September 3, until discovered by the neighbor. The circumstances and findings were believed to be sufficient to warrant a tentative diagnosis of coma due to hypoglycemia. Ten cubic centimeters of 50 per cent dextrose solution were given intravenously without

demonstrable effect at 5:45 p.m. She was removed to the hospital and admitted there at 6:45 p.m.

The following additional history was obtained from relatives after admission to the hospital. For three weeks prior to September 3, the patient had lived alone in her apartment, her mother who lived with her being out of the city on a visit. Her mother stated that several days before she vacated the apartment the patient came home from office in a daze having no recollection of how she reached there after leaving the street car which brought her from work.

Examination revealed the findings as noted above; the skin was cool, the tongue was blue, pulse was rapid and thready, breathing labored. Rectal temperature was 100° F. Blood sugar, 75 minutes after the intravenous injection, was 307 mg. Immediately after this 500 c.c. of 20 per cent dextrose in normal salt solution were given intravenously. At 8:30 p.m. the blood sugar was 500. She seemed to react favorably for a short time during the intravenous injection but returned to the comatose state. The circulation improved, the pulse slowing to 100, blood pressure rising to 140 systolic and 85 diastolic. Pupils were equal in size and moderately contracted, reacting to light. A lateral nystagmus was observed. The lower jaw moved with a chewing movement. There appeared to be some paresis of the muscles of the right side of the face and saliva drooled from the mouth. The extremities were flaccid and knee jerks absent. The Babinski and Kernig tests and ankle clonus were absent. There was some slight reaction to deep pressure over the bladder.

The bladder was catheterized and 60 c.c. of urine obtained. Except for the presence of a large amount of sugar it was normal chemically and microscopically. Spinal fluid withdrawn at 9:00 p.m. was normal, except for the total amount of sugar, 165 mg. Pressure was normal. The electrocardiogram showed no change from one done two years previously. At 9:30 p.m. a generalized convulsion lasting one minute, followed by a few minutes of spasticity, was observed. A second convulsion occurred at 10:00 p.m. At 11:00 p.m., blood chemical tests gave the following results: nonprotein nitrogen 34 mg. per cent, sugar 380 mg. per cent, carbon dioxide combining power 51 volumes per cent.

At 1:00 a.m., September 4, a convulsion lasting one minute occurred. Following this, 200 c.c. of 20 per cent dextrose in normal salt solution were given. The results of further treatment and laboratory examinations are summarized in table 2.

Neurological examination at 3:15 p.m., September 4, by Dr. Philip Litvin showed "the patient to be in coma. There was a slight lateral nystagmus, more marked to the right. The pupils alternately contracted and dilated, remaining in a somewhat contracted condition. There appeared to be some weakness of the right side of the face, but this was not definite. A flaccid paralysis of the upper and lower extremities was observed with a slightly positive Babinski test on the right, that on the left being markedly so. Impression: Cerebral infarct, probably as a result of old diabetes."

The patient's condition remained about the same on the fifth and sixth. Neurological examination on the latter date by Dr. D. D. V. Stuart, Jr., gave the following result: "Slightly contracted pupils, regular and symmetrical, which respond to light. Cervical sympathetic response intact. Slow lateral oscillatory movement of the eye balls (not a nystagmus). Corneal reflexes absent. The ocular fundi were not well seen, but there appeared to be no abnormalities of the discs or the vessels. The deep reflexes were absent. The right pectoral reflex was present and a slight movement of both feet was noted on stroking the plantar surfaces. A slight odor of acetone was noted on the breath. Impression: No clinical evidence of cerebrovascular lesion. The condition was believed to be primarily diabetic and an increased amount of insulin suggested if the spinal fluid sugar content was above 75 mg./100."

Spinal fluid removed September 8 showed 6 mm. of mercury pressure with 380 erythrocytes and 2 leukocytes per cubic millimeter. That on the tenth was under

reduced pressure with innumerable red blood cells and 10 white blood cells per cubic millimeter. The presence of free blood was believed to be due to trauma and of no clinical significance, the supernatant centrifuged fluid being colorless. The Wassermann reaction was negative.

The patient remained comatose until death occurred on September 11, at 11:30 p.m., a total of eight days. During the illness the rectal temperature gradually rose from 100° F. to 105.8°, pulse varied between 100 and 140, respirations between 20 and 30, except during the last two days, when they averaged 40 per minute. Blood pressure averaged 130 systolic, 86 diastolic during the greater part of the illness. Sweating was most profuse at all times. Beginning September 6, nourishment was

TABLE II

Date	Nourishment	Blood Chemistry						Urine			Insulin Units	Remarks
		Sugar	N.P.N.	Chlorides	Ca	Inorg. Phos.	CO_2 Comb. Power	Sugar	Acetone	Diacetic Acid		
		Mg. per 100 c.c.					Vol. %					
9/3/36												
5:45 p.m.	10 c.c. 50% dextrose (V)											
7:00 p.m.		307										
7:15 p.m.	500 c.c. 20% dextrose (V) in normal NaCl sol.	500										B.P. 140/85
8:30 p.m.												Convulsion
9:30 p.m.												Convulsion
10:00 p.m.												
10:30 p.m.			34				51	4+	0	0		
11:15 p.m.		380										
9/4/36												
2:00 a.m.	200 c.c. 20% dextrose (V) in Hartman's solution											Convulsion
8:00 a.m.		285		454	8.0	3.3		4+	0	0		B.P. 94/60, 1 gm. calcium gluconate intrav.
3:00 p.m.		324					30	4+	0	0		1 gm. calcium gluconate intrav.
8:00 p.m.	250 c.c. 5% dextrose (V) in Hartman's sol.											B.P. 112/76, R.B.C. 4,670,000, W.B.C. 21,200, Hgb. 14.8 gm./100 c.c., P. 96%, L. 4%
9:30 p.m.								3+	+	+		
12:00 p.m.								3+	+	0		
9/5/36												
12:30 a.m.											15	
4:00 a.m.								3+	+	0	15	W.B.C. 16,500, P. 96%, L. 4%, B.P. 142/94
6:00 a.m.		222					36					
8:00 a.m.								3+	+	0	15	
11:00 a.m.	1,000 c.c. 5% dextrose (V) in normal NaCl sol.										25 130	
5:00 p.m.								3+	+	0	15	B.P. 126/86
8:00 p.m.	1,000 c.c 5% dextrose (V) in normal NaCl sol.										30	
9:00 p.m.											15	
9/6/36	C 106 P 24 F 10 (by tube feedings)											
1:45 a.m.								3+	+	0	15	
5:15 a.m.								3+	+	0	15	
8:30 a.m.								0	+	0	75	B.P. 152/90
3:00 p.m.								2+	0	0	15	
7:00 p.m.								3+	0	0	15	
11:30 p.m.								3+	0	0	15	
9/7/36	C 234 P 36 F 15 (by tube feedings)											
3:00 a.m.								3+	+	0	15	
7:00 a.m.								3+	+	0	15	
11:15 a.m.		333										B.P. 140/90
12:00 a.m.								1+	0	0	105	1,000 c.c. Normal NaCl sol. subcutaneously

TABLE II—*Continued*

Date	Nourishment	Blood Chemistry						Urine			Insulin Units		Remarks
		Sugar	N.P.N.	Chlorides	Ca	Inorg. Phos.	CO_2 Comb. Power	Sugar	Acetone	Diacetic Acid			
		Mg. per 100 c.c.					Vol. %						
3:00 p.m.								3+	+	0	20		
7:00 p.m.								3+	0	0	20		
11:00 p.m.								3+	0	0	20		
9/8/36	C 204 P 54 F 54 (by tube feedings)												
3:00 a.m.								3+	+	0	20		B.P. 120/80
7:00 a.m.								3+	+	0	20		
11:00 a.m.								2+	0	0	12		1,000 c.c. Normal NaCl sol. subcutaneously
												101	
3:00 p.m.		250						3+	0	0	20		
7:00 p.m.								4+	0	0	24		
10:20 p.m.		204											
11:00 p.m.								1+	0	0	5		
9/9/36	C 204 P 54 F 54 (by tube feedings)												
3:00 a.m.								3+	0	0	20		
7:00 a.m.								3+	+	0	20		B.P. 120/88
11:00 a.m.								3+	0	0	20		1,000 c.c. Normal NaCl sol subcutaneously
3:00 p.m.								3+	0	0	20		
7:30 p.m.								3+			20	112	
12:00 p.m.								2+	0	0	12		B.P. 128/86
9/10/36	C 204 P 54 F 54 (by tube feedings)												
3:00 a.m.								3+			20		
7:00 a.m.		333	56	528			60	3+	+	0	20		B.P. 110/80
11:00 a.m.								3+	0	0	20		1,500 c.c. normal NaCl sol. subcutaneously
2:30 p.m.								1+	0	0	5		300 c.c. tap water by bowel.
												195	R.B.C. 5,330,000,000, Hgb. 15 gm./100 c.c., W.B.C. 20,000
7:00 p.m.								3+	0	0	20		P. 74%, L. 16%, Endo. 5%, Turk. 2%, Baso. 1%, Eosin. 2%
11:00 p.m.								3+	0	0	20		
9/11/36	C 266 P 39 F 39 (by tube feedings and intrav.)												
3:00 a.m.								3+	+	0	20		300 c.c. tap water by bowel.
7:00 a.m.								1+	0	0	5		B.P. 100/86, 1,500 c.c.
11:00 a.m.								3+	0	0	20	71	normal NaCl sol. subcu-
3:00 p.m.								3+	0	0	20		taneously, 300 c.c. tap
7:00 p.m.								1+	0	0	6		water by bowel, B.P. 88/
8:30 p.m.								1+	0	0			65, 1,000 c.c. 5% dextrose
11:00 p.m.													sol. intravenously. Death.
11:30 p.m.													

given by tube feedings with one liter of normal salt solution subcutaneously daily, a daily total fluid of 3,100 c.c. being given.

Necropsy was performed 11 hours after death. The findings are summarized as follows: The lungs showed passive congestion and superficial atelectasis. The heart was of normal size, the musculature being soft, and on microscopic examination giving evidence of myocardial degenerative change. The mitral valve was thickened and the coronary arteries showed moderate atheromatous changes as did the aorta. The liver was the site of fatty degeneration and chronic passive congestion. The pancreas weighed 50 gm. and was unusually soft and hyperemic. On microscopic examination there was found an increase in interstitial connective tissue, the acinar tissue being hyperplastic. Granular degeneration was marked and islet tissue was but rarely recognized. The kidneys showed parenchymatous degeneration, moderate

interstitial fibrosis, but little vascular change. The uterus was twice the normal size, due to a nodular fibroid tumor in the fundus, it being retroverted and bound down firmly to the sigmoid. The left tube and ovary were intimately enmeshed in these adhesions. *B. cloacae* was cultured from the heart's blood.

The most striking changes were noted in the brain, which externally exhibited nothing unusual. The superior surface of the pituitary body was flattened suggesting the probability of increased intracranial pressure. On section the left cerebral hemisphere showed occasional scattered punctate hemorrhagic areas within the cortex and very rarely in the deeper structures. Connected with one of the fissures in the occipito-parietal region was found a cystic space approximately 1.5 cm. in diameter, the outer portion lined by typical gray matter, the deeper portions eroded, the wall being covered by a fine fibrinous material. This space is believed to be the result of pressure from fluid accumulating within the fissure, possibly blood which was later absorbed. Section of the right hemisphere revealed more numerous punctate hemorrhages and a smaller cystic space than that described above, lying near the medial surface of the occipital lobe. No gross evidence of thrombus within or hemorrhagic infiltration outside the vessels of the internal capsule was noted.

Microscopic examination: "The right occipito-parietal lobe and the right internal capsule are markedly edematous with perivascular accumulations of fluid. The vessels appear to be sclerotic and calcification of their walls is seen. The appearance suggests a moderate increase in glial tissue. The left internal capsule is very edematous and small foci of degeneration are noted. Small extravasations of blood and some pigment is found about the vessels. Rather similar findings are observed in the left pons. Sections through the choroid plexus of the left lateral ventricle show the ependyma to be normal. The plexus is congested and edematous with some tendency to epithelial desquamation. Many arterioles are completely occluded by calcific thrombi (?), while others show no change. The left choroid plexus in the third ventricle shows similar changes, there also being calcium deposits bearing no definite relation to the blood vessels. These appear to be true psammoma. The cyst wall is represented by fragmented bodies of degenerated parenchyma presenting no evident surrounding inflammatory reaction. The cavity is lined by debris which contains many large beaded bacillary forms. In many of the adjacent blood vessels these organisms can be seen, some appearing to form thrombi. The pituitary body is markedly edematous, the basophilic elements predominating."

Comment

The history obtained from the patient, relatives and friends indicates that she probably experienced the effects of a relatively low blood sugar on a number of occasions during the late afternoon and evening or early morning over a period of two months preceding her death. Although the lowest blood sugar obtained at any time was 100 mg./100 c.c., it seems likely that lower levels were reached during some of the above mentioned periods; however, no examinations of the blood were made at any time between 5:30 p.m. and 8:00 a.m. Persons living in the same building with the patient stated that during the early part of her treatment with protamine insulin she frequently ate more than her diet called for, but that later on she closely adhered to it.

In view of the marked cerebral arteriosclerosis and the maintenance of the blood pressure at a level slightly below normal, it would appear that the patient was more than ordinarily susceptible to the effects of a relatively low blood sugar. We believe that the result of lowering the blood sugar level in this patient to a point considerably below normal would have an effect analogous to

that obtained in a diabetic individual with marked coronary artery sclerosis. Many of the physical findings observed after unconsciousness was noted, are frequently seen in coma due to insulin hypoglycemia, viz., tonic and clonic muscle spasm, lateral movements of the eyeballs and positive Babinski.

Attention is called to the similarity of this case report and Bowen and Beck's [3] case 2, with necropsy findings in the brain by Terplan.[4] White [5] also mentions the case of a child, who died as a result of hypoglycemia and on whom a complete necropsy was performed, with findings quite similar to ours. The presence of cerebral arteriosclerosis represents the most important point of difference between the pathological changes in the brain of our patient and those mentioned above. Due to the narrowing of the vessels, a reduced amount of dextrose was supplied to the brain unless the blood sugar was maintained above the usual normal. We feel that this abnormality may have caused her to react to the effects of hypoglycemia when the amount of sugar in her blood was lowered to a level which would not have brought on marked symptoms of hypoglycemia in a patient not similarly affected.

At the time of admission to the hospital in a comatose state, the blood sugar was 307 mg.; however, the next morning after a total of 145 gm. of dextrose had been given intravenously, no insulin having been administered for 24 hours, the amount in the blood was 285 mg. Although one neurological consultant felt that the patient's unconscious state was due to acidosis and insufficient insulin, we do not believe that ketosis was a significant factor at any time, inasmuch as the carbon dioxide combining power on hospitalization was 51 volumes per cent and neither acetone nor diacetic acid was present in the urine. The lowest carbon dioxide combining power recorded was 30, on the second day of coma. Diacetic acid was found in the urine once during the course of the illness, over 40 specimens being examined.

Although there is insufficient laboratory evidence to prove conclusively that the patient's coma was caused by insulin hypoglycemia, we feel that the available data strongly support the view that such a condition was an important factor in its production. The possible dangers incident to the use of any insulin preparation with prolonged action and cumulative effect are emphasized. Until the actions of such preparations are more definitely known we feel that their use should be restricted to those who can be kept under rather constant supervision and control.

Summary

1. In the case reported, the difficulties in the control of the patient's diabetes were greatly reduced following the use of protamine insulin; however, reactions attributed to insulin hypoglycemia were accentuated.

2. Unconsciousness, believed to be due to prolonged and possibly severe hypoglycemia resulting from the cumulative effect of protamine insulin, was observed.

3. Death followed eight days coma. Necropsy revealed cerebral arteriosclerosis and cerebral edema with some degenerative changes in the brain.

4. The possible dangers to the patient from the prolonged and cumulative effect of the more complex insulin preparations are noted.

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EDITORIAL

DISCREPANCY BETWEEN EXPERIMENTAL AND CLINICAL KNOWLEDGE OF THE ANTERIOR PITUITARY BODY

VAN DYCKE recently has written a book, "The Physiology and Pharmacology of the Pituitary Body," during the course of which he reviewed more than 5,000 articles. The bibliography fills 200 pages and yet contains but few references to clinical articles. What is most amazing is that practically all of these articles were written within the past 15 years. So many articles are being published in this field that it is virtually impossible for any practicing physician to keep informed regarding this rapidly accumulating knowledge. He is forced to rely on reviews, most of which are very good but all of which reflect the reviewer's sympathies and prejudices. Or he may rely on the publications of commercial houses some of which are good but many of which are cursory and misleading.

In general there are two groups of such articles. The first group comprises those published by workers in the fundamental fields of biology, chemistry, physiology, pathology, anatomy, and so on. Most of these represent excellent work, including detailed studies under carefully controlled conditions. However, an unprejudiced observer is impressed with the discrepancies existing even in this exact field. As an example one may mention the single factor of species difference. Results obtained with the use of one laboratory animal may be quite different when repeated in another laboratory with a different species. Differing methods of preparing the injected material, differing diets and environmental conditions for the animals, the use of animals of different sex or age—these and many other factors make the comparison of results very difficult. The result is that we do not know, for example, how many hormones of the anterior lobe of the pituitary can be regarded as accepted. Is there one gonadotropic hormone, or are there five? The one hormone which always has been above suspicion is the growth hormone, yet recently a voice has been raised to question its specificity.

The second group of articles in this field is that dealing with the clinical application of this knowledge. These articles as a group are far inferior to the first group mentioned. Many of them never should have been written and represent work which never should have been done. Extracts of uncertain character are injected into patients suffering from uncertain conditions and the misinterpreted results are published by undiscriminating editors. The result is extremely confusing to the clinician, particularly if he is being asked to see many patients supposedly suffering from "pituitary disease."

There are two major difficulties in attempting to evaluate the clinical application of our knowledge in this field. The first already has been touched

on, namely, the unsettled condition of our knowledge of the fundamental principles involved. It seems unwise to utilize clinically a hormone which is not understood biologically. Thyroid extract and insulin are used with good results because of the completion of fundamental studies before their use in the treatment of human beings was attempted. On the other hand, the thyrotropic and carbohydrate influencing principles of the pituitary are most interesting but much work remains for the laboratory before these substances should invade the treatment room. Van Dycke records more than 100 "hormones" now on the market which are obtained from the pituitary gland, sex glands, placenta, blood, or urine of animals or man. At the present writing no hormone from the feces is being marketed. Many of these 100 "hormones" are totally unsuited for injection into man.

The second difficulty is that we know so little about the clinical conditions which may arise from a disturbance of the pituitary. We know of acromegaly, dwarfism, Cushing's syndrome, and a few other well defined conditions. The difficulty is that these comprise such a small portion of the cases in which treatment is with pituitary hormones. The literature contains many references to the treatment of "hypopituitarism" and "hyperpituitarism." Such terms are so indefinite as to be meaningless.

Clinicians react to this situation in various ways. Some are busy utilizing "hormones" indiscriminately and are reporting their confusing results. Others have developed an inferiority complex because, in spite of genuine effort, they cannot obtain the dramatic cures which others report. Others are carefully utilizing standardized substances in the treatment of specific conditions and are reporting their negative as well as their positive results. Blessed are they! Others are simply waiting and hoping.

What can be suggested as a way to the solution of this confusion existing between experimental studies and clinical application? The first step might be for all responsible physicians to subscribe to the concluding paragraph in a recent editorial in the *Journal of the American Medical Association:* "These remarks are not intended to reflect upon the importance of the chemical and biological studies of accredited laboratories; the author is filled with admiration for such efforts. Neither do these remarks apply to the carefully controlled clinical application of accepted knowledge by competent observers; this is necessary. Rather are these remarks intended: (1) to emphasize the fact recognized by many interested observers that there is a great discrepancy between our laboratory knowledge of the hormones and their clinical application, (2) to suggest that for the present only those clinicians with facilities for critical study be encouraged to inject extracts into patients and that these men be urged to publish their negative as well as their positive results, and (3) to suggest that the large group of physicians not represented in either group mentioned above cease their unstudied injection of unknown substances into unsuspecting patients."

E. H. R.

REVIEWS

The Art of Treatment. By WILLIAM R. HOUSTON, A.M., M.D., F.A.C.P. 744 pages; 16.5 × 24 cm. The Macmillan Co., New York. 1936. Price, $5.00.

This work is described in the author's preface as a collection of the subject matter presented in a series of conferences with senior medical students and young doctors. The conference style is carried throughout and is always conducive to interest, although, at times, it does not lend itself very well to the subject.

A practical method is introduced for considering therapy in general. Diseases are grouped according to their chief method of treatment: by nursing care, specifics, psychotherapy or guidance, limitation of life, physiological consideration and experimental treatment. The common cold, typhoid fever, and most of the acute specific infectious diseases are included among those diseases treated chiefly by nursing care; lobar pneumonia, in spite of its frequent treatment by specific sera, is also included in this group. It is easy to understand that this method of presentation has many practical advantages, as repetition is largely eliminated, and therapeutic methods described in detail for one member of the group may apply with little or no modification to others.

The reviewer does not, however, agree with the author's decision in placing certain pathological conditions in the chosen groups of diseases. Thus, there seems to be no definite reason for including obesity, bronchiectasis and lung abscess among those treated by "limited living"; certainly the latter might better be grouped among those diseases treated by nursing care.

The author has evidently drawn on an extensive personal experience and his personality is reflected in his writing. There can be no doubt that he has done a valuable piece of work, especially in his discussion of therapeutic planning. The long introductory section is almost classical in its style, interest, and value.

A criticism that might be offered is that in certain cases discussion is too lengthy and actual advice too brief. For example, in outlining the treatment of exophthalmic goiter, no very definite therapeutic plan is presented, the usual time required for iodine remission is not stated, and treatment of thyroid storm and cardiac complications is not mentioned. In the section on diabetes, advice is somewhat indefinite and treatment of complicating infection is hardly mentioned. Diabetic coma is not very well discussed.

The section on psychotherapy contains many very helpful suggestions for the management of the patient, but here, as elsewhere, the author tends to digress from the subject frequently, so that information may be somewhat obscured. The absence of an adequate chapter on physical therapeutic methods is disappointing.

The writing of a textbook on therapy is one of the most difficult tasks an author can undertake, but Dr. Houston's contribution should be a valuable addition to our current texts.

T. N. C.

Diseases of the Newborn. By ABRAHAM TOW, M.D. 477 pages; 15.5 × 23 cm. Oxford University Press, New York, N. Y. 1937. Price, $6.50.

In the compilation of this work Dr. Tow has been extremely thorough. Practically all of the conditions affecting the newly born have been covered. Even such rarities as the Klippel-Feil syndrome and osteopetrosis receive attention. At times the discussion is extended beyond the neo-natal period, but only in the interests of clarification or completeness. Sufficient stress is laid upon the clinical side of the

book to make it attractive to the practitioner. The literature has been exhaustively investigated and where differences of opinion exist the conflicting views are presented in an unbiased fashion. The author states in the preface "On basis of years of experience on the newborn service at the New York Polyclinic Hospital certain opinions have been formulated and there has been no hesitancy in expressing these opinions when it was felt that they might clarify a controversial subject." Case reports are frequently used to illustrate diagnosis, prognosis or treatment of various diseases or conditions, a method felt by the reviewer to be quite valuable.

An excellent bibliography follows each chapter. The references are well chosen and contain the most modern views on the various subjects.

Adequate use has been made of illustrations, most of which deal with congenital defects, birth injuries, and the apparatus for special pediatric procedures. A number of these pictures are rather blurred as to detail, a factor which makes their value questionable.

The print is of a close small type and the pages are highly glossed, a combination that for prolonged use is rather tiring.

The defects of this volume are more than compensated by its thoroughness and by the excellent presentation. It compares very favorably with other books dealing with this subject and should be of value to both the practitioner and pediatrician.

J. E. B.

Practical Examination of Personality and Behavior Disorders. By K. E. Appel and E. A. Strecker. 219 pages; 15.5 × 22 cm. The Macmillan Company, New York. 1936. Price, $2.00.

There are many things in this book which serve to make it both an interesting and useful volume. Although the authors have presented the book ostensibly for medical students and neophytes in psychiatry, they have included material which may have a wider appeal. The volume is divided into two parts, the first of which is devoted to the study of adult patients and the second to children. The presentation is given largely in a very accessible outline form. It is noteworthy for its simple style and absence of flowery verbiage.

The chapter on "The Art and Practice of the Psychiatric Examination" is especially practical and timely. Specific directions as to how to elicit material of psychiatric interest are given by the authors, together with some warnings and safeguards to be followed by the person conducting the examination. The general impression created is that which is so well known to the trained psychiatrist, namely, that the physician does not tell the patient everything that he knows about him.

Most of the remainder of the section on adults applies principally to the study of psychotic patients. More attention might have been paid to the neurotic group. The first chapter described in the previous paragraph could have been incorporated nicely with the chapter on "Suggestions for Making the Mental Examination."

The greatest value of the work, in the opinion of the reviewer, lies in the portion devoted to the examination of children. The technic of obtaining information from the child by entering his phantasy life is especially interesting and practical. There is considerable material, too, that serves a useful purpose in acquainting medical men with what is considered the most modern advice concerning the emotional needs of childhood. In this respect the book contains more material of a prophylactic or therapeutic nature than purely diagnostic.

In all it may be said that the book would be a valuable addition to the library of every practitioner of medicine.

J. C. S.

The Diagnosis and Treatment of Diseases of the Heart. By HENRY A. CHRISTIAN, M.D., Sc.D., LL.D., Hersey Professor of the Theory and Practice of Physic, Harvard University. 373 pages; 15.5 × 24 cm. Oxford University Press, New York. 1935. Price, $6.00.

Dr. Christian writes interestingly and instructively of his experiences in regard to heart disease and its treatment. He emphasizes that the practitioner should as a rule be able to arrive at a cardiac diagnosis without the aids of costly special examinations and that these latter methods should never replace clinical knowledge based on experience. The reviewer has noted that many men of ripe clinical experience arrive at such conclusions; nevertheless he feels that sufficient knowledge is gained at times to make such studies routine in cases of heart disease when practicable. If they serve no other purpose they convince the patient, in these days of public knowledge, that his case has been studied thoroughly. The indications for electrocardiography are discussed in a brief chapter but no detailed description of this subject is offered. There is no chapter on roentgenographic examination of the heart. In the introduction the author states that this book is not written for students nor as a reference work, hence no attempt has been made to make the bibliography complete and it is assumed that the reader has some previous knowledge of the etiology, pathology, etc. of heart diseases. Chapters are included on such recent investigations as total ablation of the thyroid in the treatment of heart disease, and the recent advances in the pharmacology of digitalis. In the latter the author finds confirmation of his opinion in regard to the value of tonic doses of digitalis in the treatment of heart disease. The introduction is an essay of itself which may be read with pleasure by everyone.

W. S. L., JR.

The Diagnosis and Treatment of Chronic Diseases of the Respiratory Tract. By ELMER H. FUNK, M.D., and BURGESS GORDON, M.D. Reprinted from Oxford Monographs on Diagnosis and Treatment. 618 pages; 24.5 × 16.5 cm.; illustrated. Oxford University Press, New York. 1936. Price, $8.00.

This volume undertakes to cover the field of chronic pulmonary diseases. The authors have divided it into four main parts. Part one is devoted to a discussion of the general methods of diagnosis, the special diagnostic procedures, such as roentgen-ray bronchography, etc., and the various general and specific therapeutic procedures. Parts two, three and four take up in order diseases of the trachea, bronchi, lungs, pleura, pulmonary tuberculosis, intrathoracic new growths and diseases of the diaphragm.

The manner in which the authors treat the various subjects is briefly as follows: general discussion, etiology, pathology, clinical manifestations, physical signs, diagnosis, and treatment. Along with this are included numerous helpful roentgen-ray plates, a few case histories, and a number of valuable references.

To cover the entire field of the chronic pulmonary diseases in such a thorough and concise manner requires painstaking efforts. The authors have achieved this end admirably and present us with a volume which can be safely recommended as a clear, concise, and valuable text.

H. V. L.

COLLEGE NEWS NOTES

Gifts to the College Library

Grateful acknowledgment is made of the receipt of the following donations to the College Library of publications by members:

Books

Dr. J. N. Hall (Fellow), Denver, Colo., "Tales of Pioneer Practice";
Dr. Samuel A. Loewenberg (Fellow), Philadelphia, Pa., "Clinical Endocrinology";
Dr. Frederick R. Taylor (Fellow), High Point, N. C., a bound pamphlet containing page reprints and new material added to the chapter on "Unusual Diseases and Symptom-Complexes not Discussed in Other Chapters," from the Oxford Loose-Leaf Medicine;
United Hospital Fund of New York, Volume II of the "Hospital Survey of New York."

Reprints

Dr. Miles J. Breuer (Fellow), Lincoln, Nebr., 2 reprints—"The Ideal and the Real in Medical Practice" and "The Treatment of Chronic Infectious Arthritis";
Major J. R. Darnall (Fellow), M.C., U. S. A., 2 reprints—"War Service with an Evacuation Hospital" and "Diabetic Coma";
Dr. Jacob Gutman (Fellow), Brooklyn, N. Y., 9 reprints—
"The Use of Modern Drugs in the Treatment of Disease,"
"The Use of Modern Drugs in the Treatment of Disease, I,"
"The Use of Modern Drugs in the Treatment of Disease, II,"
"The Use of Modern Drugs in the Treatment of Disease, III,"
"The Use of Modern Drugs in the Treatment of Disease, IV,"
"The Use of Modern Drugs in the Treatment of Disease, V,"
"Endocrine Disorders of the Female Sex; Their Causes and Correction,"
"Acidosis and Alkalosis: Their Significance and Treatment" and
"Pituitary Hormones and Their Functions";
Dr. Donald S. King (Fellow), Boston, Mass., 2 reprints—"Hemorrhagic Bronchiectasis and Its Surgical Cure" and "The Middle Lobe of the Right Lung: Its Roentgen Appearance in Health and Disease";
Dr. George R. Minot (Fellow), Boston, Mass., 1 reprint—"Investigation and Teaching in the Field of the Social Component of Medicine";
Dr. William H. Ordway (Fellow), Mount McGregor, N. Y., 1 reprint—"An Interpretation of the Nature of Hodgkin's Disease";
Dr. Kenneth Phillips (Fellow), Miami, Fla., 1 reprint—"Studies on the Neutralization Test of Gastric Acidity in Relation to General Disease";
Major James Stevens Simmons (Fellow), M.C., U. S. A., 1 reprint—"Observations on the Importance of *Anopheles Punctimacula* as a Malaria Vector in Panama, and Report of Experimental Infections in *A. Neomaculipalpus, A. Apicimacula,* and *A. Eiseni*";
Dr. Clair L. Stealy (Fellow), San Diego, Calif., 1 reprint—"The Pollen Content of the Air of San Diego, California";
Dr. Hyman I. Goldstein (Associate), Camden, N. J., 1 reprint—"Some Historical Notes on Allergy."

At the 84th annual meeting of the North Carolina State Medical Society, Dr. Wingate M. Johnson (Fellow) of Winston-Salem was installed as President and Dr. James B. Sidbury (Fellow) of Wilmington was made President-Elect for the coming year.

Dr. Virgil E. Simpson (Fellow), Clinical Professor of Medicine, University of Louisville School of Medicine, delivered the Oration in Medicine at the annual meeting of the Illinois State Medical Association on May 18, 1937.

The third annual meeting of the Federation of American Sanatoria (a national association of chest physicians) was held at Atlantic City, N. J., June 7 to 11, under the Presidency of Dr. William Devitt (Fellow), Allenwood, Pa. Dr. Edward W. Hayes (Fellow), Monrovia, Calif., was installed as the new President. Dr. Frank Walton Burge (Fellow), Philadelphia, Pa., was Chairman of the Committee on General Arrangements; Dr. Clyde M. Fish (Fellow), Pleasantville, N. J., was Chairman of the Committee on Entertainment. The Vice-Presidents of the Federation for the past year included Dr. Charles H. Cocke (Fellow), Asheville, N. C.; Dr. Louis Mark (Fellow), Columbus, Ohio; Dr. George Foster Herben (Fellow), Loomis, N. Y.; Dr. Ralph C. Matson (Fellow), Portland, Ore.; and Dr. Samuel H. Watson (Fellow), Tucson, Ariz. Dr. Charles M. Hendricks (Fellow) of El Paso, Texas, is Chairman and Editor-in-Chief of the Federation's journal.

At the opening administrative session, addresses were made by Drs. Burge, Devitt and Hayes. Dr. J. Arthur Myers (Fellow), Minneapolis, Minn., delivered the address at the luncheon meeting on June 7. Dr. Marcus W. Newcomb (Fellow), Browns Mills, N. J., delivered an address on "The Early Diagnosis of Pulmonary Tuberculosis"; Dr. Frank Walton Burge (Fellow), Philadelphia, delivered an address on "Bronchography." Dr. William Egbert Robertson (Fellow), Philadelphia, was a guest speaker at the Banquet, at which Dr. William C. Voorsanger (Fellow), San Francisco, was the toastmaster.

Dr. Anita M. Mühl (Fellow), San Diego, Calif., has recently completed her postgraduate work at Johns Hopkins University and is spending an indefinite period in Europe. She will attend the Medical Women's International Association convention at Edinburgh, Scotland, July 12 to 18, and the Second International Congress on Mental Hygiene in Paris, France, the week following.

Dr. Thomas B. Magath (Fellow) of the Mayo Clinic has been appointed Health Officer of the city of Rochester. He succeeds Dr. Charles H. Mayo who has been Health Officer for twenty-five years.

The Council on Diabetes of the Public Health Federation, of which Dr. Cecil Striker (Fellow) is Chairman, had a "Diabetic Day" with clinics in the morning and a round table luncheon meeting and a meeting of the Academy of Medicine of Cincinnati. Dr. Russell M. Wilder of the Mayo Clinic discussed the medical aspects of diabetes and Dr. A. W. Allen of the Massachusetts General Hospital the surgical aspects.

Dr. Cecil Striker was guest speaker of the Ohio State Dietetics Association, April 13, at Columbus, Ohio, where he spoke on "Newer Concepts in Diabetes."

The Kansas section of the American College of Physicians met at the Menninger Clinic, 3617 West Sixth Avenue, Topeka, Kansas, Thursday, May 20. Dr. Thomas

T. Holt of Wichita, Governor of the American College of Physicians for Kansas, presided. Members who attended were Dr. William H. Algie of Kansas City, Kansas, Dr. Ralph Ball of Manhattan, Dr. James A. Butin of Chanute, Dr. Arthur Revell of Pittsburg, Dr. Harold Jones of Winfield, Dr. Harold Palmer of Wichita, Dr. George F. Corrigan of Wichita, Dr. Kenneth L. Druet of Salina, Dr. Paul M. Krall, of Kansas City, Kansas, Dr. Fred McEwen of Wichita, Dr. Philip Morgan of Emporia, Dr. G. A. Westfall of Halstead, and Dr. W. C. Menninger of Topeka.

Papers given were: Demonstration of Neurological Cases by Drs. Norman Reider and Harry Roback, Topeka. "Psychological Conflicts Expressed in Physical Symptoms: Case Studies" by Dr. Robert P. Knight, Topeka. "Gastrointestinal Neuroses" by Dr. W. C. Menninger, Topeka. "The Clinical Application of Endocrine Therapy" by Dr. Ralph Ball, Manhattan. "Undulant Fever" by Dr. Wm. H. Algie, Kansas City, Kansas. "Reports of Some Unusual Cardiac Cases" by Dr. Fred McEwen, Wichita. "Some Aspects of a Group of Patients Who Were Examined on the Suspicion of Heart Disease" by Dr. Philip Morgan, Emporia. "Impotence and Frigidity" by Dr. Karl A. Menninger, Topeka.

In addition to the members, many guests attended the program. Out of town guests of the Section included: Dr. Frank Moorhead of Neodesha, Dr. George Seitz of Salina, Dr. R. R. Sheldon of Salina, Dr. N. P. Sherwood of Lawrence, Dr. Maurice Snyder of Salina, Dr. Charles Underwood of Emporia, Drs. Frank Koenig and John Russell of Osawatomie, Dr. Earl Vermillion of Salina, Dr. M. W. Husband of Manhattan, Dr. Ralph I. Canuteson of Lawrence, Dr. Henry Benning of Waverly, and Dr. Allen Olson of Wichita.

Topeka doctors who attended were: Dr. R. B. Stewart, Dr. Lucius E. Eckles, Dr. Leslie Saylor, Dr. F. A. Taggart, Dr. J. A. Crabb, Dr. C. F. Menninger, Dr. Robert P. Knight, Dr. C. W. Tidd, Dr. Norman Reider, Dr. Karl A. Menninger, Dr. C. C. Carlson, Dr. Bernard Kamm, Dr. William C. Menninger, Dr. Martin Grotjahn, Dr. H. N. Roback, Dr. Byron L. Shifflet, Dr. Joseph Pessin, Dr. Robert T. Morse, and Dr. Eugene Eisner.

The program began at ten in the morning and continued all day with a barbecue supper at Indian Hill, Dr. Karl Menninger's country home, in the evening.

Dr. William Paul Holbrook (Fellow), Tucson, has been elected Vice-President of the Arizona State Medical Association.

Dr. Francis G. Blake (Fellow and College Governor for Connecticut), Sterling Professor of Medicine, Yale University School of Medicine, was a guest speaker at the annual scientific assembly of the Medical Society of the District of Columbia on May 5 and 6, his subject being "Serum Therapy in Pneumonia." Other members of the College participating on the program were Dr. Arthur C. Christie (Fellow), Washington, "The Socialization of Medicine: To What Extent Is It Desirable?"; Dr. Walter Freeman (Fellow), Washington, "The Surgical Treatment of Mental Disorders"; and Dr. Henry B. Gwynn (Associate), Washington, "Artificial Fever Therapy of Gonorrheal Arthritis."

Dr. Charles Franklin Craig (Fellow), Professor of Tropical Medicine, Tulane University of Louisiana School of Medicine, New Orleans, addressed the eighty-eighth annual session of the Medical Association of Georgia at Macon, May 11 to 14, on "Tropical Diseases of Interest to Southern Physicians."

The seventy-eighth annual session of the Kansas Medical Society was held at Topeka, May 3 to 6. The following Fellows of the College were guest speakers:
Dr. Elliott P. Joslin, Boston, "The Diabetic as a Surgical and an Obstetrical Risk";
Dr. Archibald L. Hoyne, Chicago, "Progress in the Treatment of Meningococcic Meningitis";
Dr. Russell L. Haden, Cleveland, "Clinical Approach to the Rheumatic Problem."

Dr. Philip W. Brown (Fellow), Rochester, Minn., presented a lecture on "The Management of Diarrheas" before the annual graduate assembly of the Harrisburg (Pa.) Academy of Medicine, May 27.

Sir Frederick G. Banting (Fellow), Toronto, Ont., was one of the speakers on the symposium on recent progress in science on the occasion of the dedication of the new building of the Mellon Institute for Industrial Research in Pittsburgh early in May.

Dr. William S. Middleton (Fellow), Madison, Wis., and Dr. Logan Clendening (Fellow), Kansas City, Mo., presented papers on "William Wood Gerhard" and "The Medical Winning of the West," respectively, before the thirteenth annual meeting of the American Association of the History of Medicine at Atlantic City, N. J., May 3. The meeting commemorated William Wood Gerhard's differentiation of typhus from typhoid one hundred years ago.

Dr. Rufus I. Cole (Fellow), New York City, addressed the annual Conference of State and Provincial Health Authorities of North America at Washington, D. C., April 5 to 6, on "Possibilities for Pneumonia Control as Indicated by Present Scientific Knowledge."

Dr. William H. Walsh (Fellow), Chicago, addressed the Tri-State Hospital Assembly, sponsored by the hospital associations of Illinois, Indiana and Wisconsin, at Chicago, May 5 to 7, on "Correct Designing of a Medical Record Library."

Dr. Israel Davidsohn (Associate), Chicago, was a speaker at the annual banquet, sponsored by the Chicago Hospital Association, his subject being "Infectious Mononucleosis: Its Hematologic and Serologic Diagnosis."

Dr. Rafael Rodriguez Molina (Fellow), San Juan, Puerto Rico, has been elected Secretary of the Puerto Rico chapter of the Pan American Medical Association.

Dr. William R. Brooksher (Fellow), Fort Smith, Ark., has been reëlected Secretary of the Arkansas Medical Society for 1937 to 1938.

Dr. George E. Wakerlin (Fellow) has been appointed Professor and Head of the Department of Physiology at the University of Illinois College of Medicine, effective September 1. Dr. Wakerlin has been Professor of Pharmacology and Physiology at the University of Louisville School of Medicine, Louisville, Ky.

Dr. Ralph M. Fellows (Fellow), Superintendent of the Osawatomie (Kan.) State Hospital, has been elected Vice-President of the Kansas Society for Mental Hygiene.

Dr. Walter C. Alvarez (Fellow), Rochester, Minn., addressed the seventieth annual session of the Mississippi State Medical Association at Meridian, Miss., May 11 to 13, on "Helpful Hints in the Diagnosis of Gastro-Intestinal Diseases."

Dr. Clarence M. Hyland (Fellow), Los Angeles, addressed the Nebraska State Medical Association at Omaha, May 10 to 13, on "The Convalescent Serum Center and Its Value to the Community."

Dr. Anton J. Carlson (Fellow), Chicago, spoke upon "Facts and Fallacies of Organotherapy" before the one hundred and forty-sixth annual meeting of the New Hampshire Medical Society at Manchester, May 18 to 19.

Dr. Meldrum K. Wylder (Fellow), Albuquerque, has been appointed a member of the State Board of Public Health of New Mexico.

Dr. James C. Walsh (Associate), Superintendent of the Schenectady (N. Y.) County Tuberculosis Hospital, has accepted an appointment as Superintendent of the Nassau County Sanatorium at Farmingdale, N. Y.

Dr. Charles A. Elliott (Fellow), Chicago, addressed the forty-fifth annual session of the Oklahoma State Medical Association at Tulsa, May 10 to 12, on "Management of Cardiovascular Disease; Management of Hepatic Disease." He also addressed the section on general medicine on "Management of Edema."

The Rhode Island Medical Society sponsored a series of lectures open to the public during the month of March. Dr. Charles F. Gormly (Fellow), Providence, delivered one on the subject "How to Grow Old Gracefully" and Dr. Henry L. C. Weyler (Associate), Providence, gave one on "Why Poison Yourself—The Nostrum Evil."

Dr. Edgar A. Hines (Fellow), Seneca, has been reëlected Secretary of the South Carolina Medical Association for 1937 to 1938.

Dr. Malcolm T. MacEachern (Fellow), Chicago, will address the fifth International Hospital Congress in Paris, July 5 to 12.

Dr. Harry S. Bernton (Fellow), Professor of Hygiene, Georgetown University School of Medicine, Washington, D. C., has been appointed clinical specialist in allergy in the bureau of chemistry and soils of the U. S. Department of Agriculture.

Dr. Porter P. Vinson (Fellow), Richmond, Va., and Dr. Charles Sidney Burwell (Fellow), Boston, Mass., were guest speakers on the program of the one hundred and forty-fifth annual meeting of the Connecticut State Medical Society at Bridgeport, May 19 to 20. Dr. Vinson spoke on "Diagnosis and Treatment of Primary Malignant Disease of the Tracheobronchial Tree" and Dr. Burwell's title was "Factors in the Treatment of Asymptomatic Period of Heart Disease."

Dr. William B. Castle (Fellow), Boston, and Dr. Cyrus C. Sturgis (Fellow), Ann Arbor, Mich., were guest speakers at the one hundred and thirty-first annual meeting of the Medical Society of the State of New York at Rochester, May 24 to 26.

Dr. Louis B. McBrayer (Fellow), Southern Pines, has resigned as Secretary and Treasurer of the Medical Society of the State of North Carolina. He has been made honorary Secretary for life. Dr. McBrayer served as President of the Medical Society of the State of North Carolina, and had been its Secretary and Treasurer for twenty-one years. The Society, in appreciation of his long service, gave a dinner in his honor, at which a silver service was presented. Dr. Paul H. Ringer (Fellow), Asheville, was toastmaster.

Dr. Edward L. Tuohy (Fellow and College Governor for Minnesota), Duluth, addressed the fiftieth annual session of the North Dakota State Medical Association at Grand Forks, May 16 to 18, and was the principal speaker at the annual banquet.

Dr. Oscar B. Biern (Fellow), Huntington, delivered the annual oration in medicine on "The Value of the Sedimentation Rate in Medicine" at the seventieth annual meeting of the West Virginia State Medical Association at Clarksburg, May 24 to 26. Other guest speakers included Dr. Horton R. Casparis (Fellow), Nashville, Tenn., "Mental Health of Children; Pediatric Responsibility in Health Education"; Dr. Louis F. Bishop, Jr. (Fellow), New York City, "Prevention of Heart Disease; Fugitive Arrhythmias"; Dr. Moses Paulson (Fellow), Baltimore, "Newer Aspects of Gallbladder Disease of Practical Import"; and Dr. Thomas Parran (Fellow), Surgeon General, U. S. Public Health Service, "Public Health Control of Syphilis."

Dr. Edward S. Sledge (Fellow), Mobile, was elected President of the Medical Association of the State of Alabama on April 22.

Dr. John A. Sevier (Fellow), Colorado Springs, is President of the Colorado Tuberculosis Association.

Dr. William G. Herrman (Fellow), Asbury Park, was installed as President of the Medical Society of New Jersey at its annual meeting in Atlantic City April 28.

Dr. Rufus I. Cole (Fellow), Director of Hospitals of the Rockefeller Institute for Medical Research, New York City, has been announced as the recipient of the George M. Kober Medal by the Association of American Physicians for next year.

Dr. Cole has announced that he will retire June 30, on account of age, as Director of the Hospital of the Rockefeller Institute for Medical Research. Dr. Cole has been Director since 1909. He is a native of Rowsburg, Ohio, took his medical degree at Johns Hopkins University School of Medicine, 1899, and served in various capacities at Johns Hopkins Hospital from 1899 to 1907 and at the medical school from 1901 to 1909. He was President of the Association of American Physicians in 1931. He received the honorary degree of Doctor of Science from the University of Chicago in 1927. He has been a prolific contributor to medical literature and is a member of many national societies.

Dr. Walter M. Simpson (Fellow), Dayton, Ohio, was made a member of the Legion of Honor of France, in recognition of his research on artificial fever.

Dr. Charles E. Sears (Fellow), Portland, has been elected President of the Oregon State Medical Society for 1937 to 1938.

Dr. William D. Stroud (Fellow and Treasurer) was reëlected President of the Philadelphia Heart Association, April 28. Dr. Samuel A. Levine (Fellow), Boston, was a guest speaker at the meeting and Dr. David Riesman (Fellow), Philadelphia, as Chairman of the Executive Committee, reviewed the year's work.

Dr. William S. Middleton (Fellow), Madison, Wis., has been appointed Chairman of the Council on Scientific Work of the State Medical Society of Wisconsin. This committee supersedes the program committee.

Dr. William F. Lorenz (Fellow), Madison, has been appointed Chairman by Governor La Follette of a "planning council" to develop a program for the control of venereal disease in Wisconsin.

Dr. Thomas Parran (Fellow), Surgeon General of the U. S. Public Health Service, gave as his Presidential Address "The Present Needs in the Public Health Control of Gonorrhea" before the American Neisserian Medical Society at Atlantic City, June 8.

Under the Presidency of Dr. Roy R. Kracke (Fellow), Emory University, Ga., the American Society of Clinical Pathologists held its sixteenth annual meeting at Philadelphia, June 2 to 5. Dr. Kracke's Presidential Address was on "The Future of Pathology."

Dr. Jabez H. Elliott (Fellow and College Governor for the Province of Ontario), Toronto, participated in a symposium on the evolution of tuberculosis dispensary control at the thirty-third annual meeting of the National Tuberculosis Association at Milwaukee, Wis., May 31 to June 3.

OBITUARIES

DR. OTIS SUMTER WARR

Dr. Otis S. Warr, a Fellow of the College, died in Knoxville, Tennessee, on March 22, 1937, of lobar pneumonia which developed while on a trip through the Great Smoky Mountain National Park.

Dr. Warr was born in Darlington, South Carolina, April 30, 1881. His preliminary educational advantages were those of the common school of his home community and later he attended the George Peabody College at Nashville, Tennessee. He was graduated in medicine from the University of Nashville Medical College in 1907, and following this spent the next four years as intern in several hospitals including Bellevue Hospital in New York.

At the conclusion of his internship Dr. Warr pursued two years of post-graduate study at Harvard and in Vienna—his work in the latter city being interrupted by the outbreak of the World War. On his return home he located in Memphis, Tennessee, where he soon became one of the outstanding internists. With the entry of the United States in the World War his application for service in the U. S. Army was declined on physical grounds but being anxious as always to do his bit he devoted much time to service on one of the medical advisory boards.

Early in his career Dr. Warr became actively interested in medical organization work. He became a Fellow of the College in 1920; was active in the formation of the Mid-South Post-Graduate Assembly held annually in Memphis. At the time of his death he was President of the Memphis and Shelby County Medical Society. For a number of years he served as Chairman of the Committee on Education of the Tennessee State Medical Association and it was due largely to his vision and energy and effort that the present two year program of Post-Graduate instruction in Obstetrics was provided for the rural practitioner throughout Tennessee.

As a physician Dr. Warr was outstanding—not only doing a large volume of private and consultation work but doing it unusually capably and well. Early in his professional career he became connected with the Medical Department of the University of Tennessee and his ability as a clinical teacher was such that at the time of his death he had risen to the rank of Clinical Professor of Medicine. A close student of the problems of diagnosis he was a frequent contributor to medical journals and to the programs of medical societies.

But those who had the privilege of knowing Otis Warr will remember him not only as an excellent clinician and teacher but even more as a fine gentleman in whom courage, fairness, loyalty, kindness and sympathy were so outstanding that friendship and association with him were not only real pleasures but inspirations as well.

J. O. MANIER, M.D., F.A.C.P.,
Governor for Tennessee.

DR. ISAAC SURNAMER

Dr. Isaac Surnamer (Fellow), 345 Broadway, Paterson, N. J., died April 23, 1937, of coronary thrombosis and cerebral hemorrhage, at the age of 64.

Dr. Surnamer was born in Riga, Latvia, formerly a part of Russia, October 25, 1872. He obtained his preliminary education in the Hildas Heimer Seminary in Berlin, Germany, and graduated from the Gymnasium at Berlin. From Berlin, he entered the Medical Department of the New York University from which he graduated as M.D. in 1896. In 1903, he took a post-graduate course in the clinics of Germany and in 1916 at Fordham University. He was consulting neurologist and psychologist at the Paterson General Hospital, the Paterson City Hospital and the Valley View Sanatarium for over 30 years, and was serving in that capacity at the time of his death. He was also Lecturer in Neurology at the Paterson General Hospital and the Hackensack General Hospital.

He was a member of the Passaic County Medical Society; the Medical Society of New Jersey, and a Fellow of the American Medical Association.

He was the first President of the Miriam Barnett Free School of Paterson, but was forced to resign several years ago because of declining health.

Dr. Surnamer is survived by his wife, Anna Blumberg Surnamer, and two sons, Masso M. and Bertram S. Surnamer.

He was greatly beloved by his community and profession and those who knew him have suffered a great loss in his death.

CLARENCE L. ANDREWS,
Governor for New Jersey.

DR. EUGENE SMITH DALTON

Dr. Eugene Smith Dalton died suddenly on April 19, 1937, of coronary thrombosis, at his home in Brooklyn, N. Y.; aged 55 years. Besides his wife, Jessie Brown Dalton, he is survived by a son, a daughter and one brother.

Receiving his early education in the public schools of Syracuse, N. Y., he later entered Syracuse University and Syracuse Medical School, from which he obtained his medical degree in 1908. While in college, Dr. Dalton was outstanding in athletics and an active member of the Psi U and Nu Sigma Nu Fraternities.

After the completion of his medical course, he interned at the City Hospital in New York City, where, under the training of such noteworthy teachers as Edward Janeway, Harlow Brooks, and Evan Evans, he acquired much of the thoughtful professional philosophy which characterized his career. Following this, and a year's residency at the Willard Parker Hospital for Contagious Diseases, he entered the practice of medicine in Brook-

lyn, N. Y., devoting his attention almost from the beginning to the problems of internal medicine.

Dr. Dalton's professional career in Brooklyn could be looked upon as the ideal of medical success. His ability and his professional influence grew steadily. In his younger years he served as Attending Physician at the Kingston Avenue Hospital (for Contagious Diseases) and in 1916 was appointed Assistant Attending Physician at the Methodist Episcopal Hospital and became Attending Physician at the same institution ten years later. Although never a prolific writer, Dr. Dalton was an active participant in medical affairs and a ready commentator. In addition to being a member of the A.M.A. and the associated county and state societies, he was also a member of the Associated Physicians of Long Island, the Brooklyn Society of Internal Medicine, the American Heart Association and since 1929 a Fellow of the American College of Physicians. In addition to his many medical associations, he was a member of the Flatbush Chamber of Commerce and for twenty-five years was an active Mason. His favorite recreations consisted of hunting and fishing and, as a member of the Malone Fish and Game Club and the National Rifle Association of America, he was well known as an expert in these diversions.

Dr. Dalton was looked upon as a physician of unusually sound judgment, exacting and thorough in his methods. Beyond this he was a man of broad sympathies, of unflagging devotion to duty and of compelling sincerity and intellectual honesty.

The above information has been supplied by Dr. Alexis T. Mays, F.A.C.P., a former associate of Dr. Eugene Smith Dalton.

C. F. Tenney, M.D., F.A.C.P.,
Governor for Eastern New York.

ABSTRACT OF THE MINUTES

ANNUAL BUSINESS MEETING

AMERICAN COLLEGE OF PHYSICIANS

St. Louis, April 22, 1937

The Annual Business Meeting of the American College of Physicians was held at St. Louis, April 22, 1937, with Dr. Ernest B. Bradley, President, presiding. Abstracted minutes of the preceding Annual Business Meeting held in Detroit, 1936, were read by the Executive Secretary, and by resolution approved.

President Bradley read the following report from the Board of Regents: "It is the feeling of the Regents that the standards for admission to the College should be progressively raised. A change in the By-Laws making certification by the American Board of Internal Medicine a prerequisite to Associateship was considered in recent months by the Board. It was felt, however, that this would at this time constitute too radical an increase in the requirements, and so this proposed amendment has been withdrawn. After further consideration, other proposals for increasing the standards will be submitted to the College.

"Another amendment discontinuing the admission to the College of physicians working in fields allied to internal medicine has likewise been withdrawn by the Regents. It is the present feeling of the Regents that the admission of a certain number of Fellows representing these allied specialties would be desirable. Any application for Fellowship in this class should be scrutinized with especial care and should ultimately require the certification of each candidate by his own special certifying Board, or, lacking that, its equivalent in professional or scientific achievement."

Dr. William D. Stroud, Treasurer, presented the following report, which, on resolution, was regularly approved:

Treasurer's Report for 1936

"To the Members of the American College of Physicians:

As of March 31, 1937, the College has invested securities of a book value amounting to $101,857.00; of this amount $58,853.00 is in the Endowment Fund, and $43,004.00 is in the General Fund; $82,250.00 or 80.75 per cent of the above amount is invested in bonds; $4,741.00, or 4.65 per cent, is invested in preferred stocks, and $14,866.00, or 14.6 per cent, is invested in common stocks. In addition, the College has in bank balances $47,470.00, making a total of $149,328.00, as compared with a total of $157,329.00 approximately one year ago at the time of the last yearly meeting.

"Thus, you see in spite of purchasing our new home for $52,500.00, and spending $10,000.00 on furnishings and alterations, our total funds at the present time are only $8,000.00 less than one year ago."

Mr. E. R. Loveland, the Executive Secretary, made a brief report on the activities of his office, but omitted the statistical data customarily presented because these had been given by the President on the evening of the Convocation. The complete financial statements and auditor's report for 1936 follow these Minutes.

President Bradley, before laying down the gavel of office as President, thanked the members of the College, the Regents and the Governors for their coöperation, help and advice during his term of office.

At this point, Dr. James H. Means of Boston was inducted as President. Dr. Means spoke at length concerning his aims during the coming year, and bespoke the help and advice of the members everywhere.

Dr. William Gerry Morgan, Secretary General, on behalf of the College, presented to Dr. Ernest B. Bradley, retiring President, a silver, engraved ferruled gavel "as a token of the profound appreciation of the rank and file of the College for the masterly way in which you have served as President." The gavel was accepted by Dr. Bradley with an expression of appreciation and thanks.

President Means, now occupying the chair, called for the report of the Committee on Nominations for 1937, which was presented, as follows, by Dr. George Morris Piersol, Chairman:

REPORT—COMMITTEE ON NOMINATIONS

For the Year 1937–38

A. Nominations for the Elective Offices (already published in the March issue of the ANNALS OF INTERNAL MEDICINE as provided in the By-Laws):

President-Elect .....William J. Kerr, San Francisco, Calif.
First Vice-President .....David P. Barr, St. Louis, Mo.
Second Vice-President .....G. Gill Richards, Salt Lake City, Utah
Third Vice-President.....William Gerry Morgan, Washington, D. C.

B. Nominations for the Board of Regents:

Term Expiring 1939

Walter L. Bierring, Des Moines, Iowa (to fill unexpired term of Luther F. Warren, deceased)

Term Expiring 1940

Ernest B. Bradley, Lexington, Ky.
Roger I. Lee, Boston, Mass.
Sydney R. Miller, Baltimore, Md.
Walter W. Palmer, New York, N. Y.
O. H. Perry Pepper, Philadelphia, Pa.

C. Nominations for the Board of Governors:

Term Expiring 1938

Francis G. Blake, CONNECTICUT, New Haven (to fill unexpired term of Henry F. Stoll, deceased)
Harry L. Arnold, HAWAII, Honolulu
John L. Calene, SOUTH DAKOTA, Aberdeen

Term Expiring 1939

Hugh A. Farris, MARITIME PROVINCES, St. John, N. B., Can.

Term Expiring 1940

Fred W. Wilkerson .....Alabama, Montgomery
Fred G. Holmes .....Arizona, Phoenix
Lewis B. Flinn .....Delaware, Wilmington
Turner Z. Cason .....Florida, Jacksonville
Glenville Giddings .....Georgia, Atlanta
James G. Carr .....Northern Illinois, Chicago
C. W. Dowden .....Kentucky, Louisville
Edwin W. Gehring .....Maine, Portland
Henry M. Thomas, Jr. .....Maryland, Baltimore
G. W. F. Rembert .....Mississippi, Jackson
Louis H. Fligman .....Montana, Helena
LeRoy S. Peters .....New Mexico, Albuquerque
Charles F. Tenney .....Eastern New York, New York
A. B. Brower .....Ohio, Dayton
T. Homer Coffen .....Oregon, Portland
Charles T. Stone .....Texas, Galveston
Rock Sleyster .....Wisconsin, Wauwatosa
Ramon M. Suarez .....Puerto Rico, San Juan
Fred Todd Cadham .....Manitoba, Winnipeg, Can.

Respectfully submitted,
Committee on Nominations
William B. Breed,
James D. Bruce,
Charles T. Stone,
Charles F. Martin,
George Morris Piersol, *Chairman*

After the receipt of the above report, Chairman Means called for nominations from the floor. None were made. Upon motion from the floor, duly seconded and regularly adopted, it was Resolved, that the nominations be closed; whereupon Chairman Means declared all the candidates on the report of the Nominating Committee elected.

Upon motion by Dr. C. W. Dowden, seconded and carried, it was

Resolved, that the cordial thanks of the American College of Physicians be extended to the retiring President, Dr. Ernest B. Bradley; to the General Chairman, Dr. David P. Barr, and to the members of his committees, individually and collectively, for their faithful work in the preparation and conduct of the St. Louis Session; to the Ladies Entertainment Committee for their efficient and courteous entertainment of the visiting ladies; to the medical schools and hospitals of St. Louis for putting their facilities at the disposal of the College and for their helpful participation; to the Women's Auxiliary of the St. Louis Medical Society for providing automobiles; to the St. Louis Convention Bureau and its Director for their continuous and efficient assistance; and to the Jefferson Hotel and its Convention Manager for their cooperation.

Adjournment.

Attest: E. R. Loveland,
Executive Secretary

Elections of Secretary General and Treasurer

At a meeting of the Board of Regents at St. Louis on April 23, 1937, Dr. George Morris Piersol of Philadelphia was elected Secretary General, and Dr. William D. Stroud of Philadelphia was reëlected Treasurer for 1937–38.

Executive Secretary's Report on Operation

1936

The auditor's report of his examination of the accounts of the College is hereto attached. The statements disclose a continued improvement, as shown by the following:

1932 Surplus	$ 10,598.08
1933 Surplus	5,801.06
1934 Surplus	16,160.07
1935 Surplus	17,182.09
1936 Surplus	24,948.53

The 1936 surplus was distributed as follows:

Endowment Fund	$ 3,503.10
General Fund	21,445.43
	$ 24,948.53

The total principal of the two Funds on December 31, 1936, was

Endowment Fund	$ 61,784.82
General Fund	119,832.90
	$181,617.72

One liquidating dividend of $1,949.29 was received from the Bank of Pittsburgh, reducing the balance now in depositories of banks in hands of receivers to $6,292.39.

A condensed comparison of income and expenditures for 1934, 1935 and 1936 appears on the following page. Only a Supplement to the 1935 Directory of the College was published during 1936, which accounts for the material decrease in this item over 1935, when a complete Directory was published.

The Executive Offices have been conducted conservatively, with expenditures held to a minimum for effective operation. The budgets for 1937 were approved by the Board of Regents December 13, 1936.

Respectfully submitted,

(Signed) E. R. Loveland,
Executive Secretary

January 1, 1937

A condensed comparison of income and expenditures for 1934, 1935 and 1936

General Fund

Income:	*1934*	*1935*	*1936*
Annual Dues	$20,875.35	$21,569.88	$23,070.95
Initiation Fees	6,142.32	9,479.50	11,455.00
Interest on Investments	3,117.89	1,852.54	2,358.02
Interest on Bank Balances	22.50		
Profit on Sale of Securities	1,178.39		1,077.04
Subscriptions, Annals of Internal Medicine	19,528.05	21,102.43	22,320.43
Advertising, Annals of Internal Medicine	4,455.28	5,353.89	6,014.06
Exhibits, Annual Clinical Session	6,124.85	12,361.02	6,291.04
Guest Fees, Annual Clinical Session	448.00	417.25	297.00
Miscellaneous Income	67.38	200.75	297.75
	$61,960.01	$72,337.26	$73,181.29

Expenditures:			
Annual Clinical Session	$11,646.40	$14,139.26	$ 9,975.84
Annals of Internal Medicine	19,216.05	21,373.02	23,667.54
Executive Secretary's Office	15,647.70	16,343.00	16,175.03
New College Headquarters, Maintenance, etc.			1,381.64
1935 Directory		3,548.33	205.68
Loss on General Fund Investments Sold		149.63	
John Phillips Memorial Prize		840.26	*
Miscellaneous	624.79	703.39	983.10
	$47,134.94	$57,096.89	$52,388.83

Endowment Fund

Income:			
Profit on Investments, sold and matured			$ 418.10
Interest on Investments	$ 2,311.63	$ 2,115.79	2,242.21
Income from Cash in Savings Accounts		135.52	
Life Membership Fees	1,710.00	2,615.00	3,085.00
	$ 4,021.63	$ 4,866.31	$ 5,745.31
Expenditures:			
*John Phillips Memorial Prize			$ 75.13
Research Fellowship	$ 450.00	$ 2,250.00	1,514.11
Loss on Investments Called		53.28	
	$ 450.00	$ 2,303.28	$ 1,589.24

H. I. MacLean,

309 Valley Road,

Llanerch, Pa.

March 28, 1937

To the Board of Regents,
American College of Physicians, Inc.,
Philadelphia, Pa.

Mr. E. R. Loveland, Executive Secretary

Dear Sirs:

I have examined the accounts of the

American College of Physicians, Inc.

for the year ended December 31, 1936, and the accompanying statements, including the Balance Sheet at December 31, 1936, the analyses of the General Fund and the Endowment Fund, and the Detailed Statement of Operations for the year ended December 31, 1936, are in accordance with the books of account and in my opinion set forth correctly the financial position at December 31, 1936, and the results of operations for the calendar year ended December 31, 1936, subject to the following comments:

Cash: The cash was properly accounted for. The following is a statement of the cash in the various depositories:

Girard Trust Company, Philadelphia	$11,093.50
Provident Trust Company, Philadelphia	5,661.47
Royal Bank of Canada, Montreal	741.82
Philadelphia Saving Fund Society (Time Deposit)	2,648.37
Western Saving Fund Society (Time Deposit)	2,648.49
	$22,793.65

The amount of cash in closed banks at January 1, 1936, was $8,241.68; during the year a liquidating dividend amounting to $1,949.29 was received, which reduced the amount to $6,292.39, as shown by the following schedule.

	Balance Jan. 1, 1936	*Liquidating Dividend*	*Balance Dec. 31, 1936*
Bank of Pittsburgh, Pittsburgh	$3,411.26	$1,949.29	$1,461.97
Exchange National Bank, Pittsburgh	1,749.20		1,749.20
Highland National Bank, Pittsburgh	3,081.22		3,081.22
	$8,241.68	$1,949.29	$6,292.39

Accounts Receivable: The accounts receivable were examined and found to be less than one year old and appear to be good and collectible. The detailed accounts receivable were in agreement with the control account. The amount due from broker of $2,180.31 represents the proceeds from the sale of 30 Shares of Steel Corporation of Canada, 7 per cent, preferred stock, and was confirmed by correspondence with Hornblower & Weeks. In accordance with the action of the Board of Regents, the amount advanced on account of expenses of the American Board of Internal Medicine has been recorded as an accounts receivable. No requests for confirmation of the other accounts were mailed.

Investments: The securities were accounted for by direct correspondence with the Girard Trust Company of Philadelphia and the income for the period under review was verified. It is noted that the uninvested principal and income cash of the Endowment Fund has been segregated from the General Fund cash on the books of account of the College.

General: The increase in the amount of the Endowment Fund and the General Fund during the year 1936 is as follows:

	Balance Dec. 31, 1935	*Net Increase*	*Balance Dec. 31, 1936*
Endowment Fund	$ 58,281.72	$ 3,503.10	$ 61,784.82
General Fund	99,047.47	20,785.43	119,832.90
	$157,329.19	$24,288.53	$181,617.72

In accordance with the instructions of the Executive Secretary, the prepaid insurance at December 31, 1936, was not set up as a deferred expense; the other deferred and accrued items were verified; the charges to the College Headquarters account were examined and included the amount paid for the property at 4200 Pine Street, settlement charges, alteration and improvement costs and other expenses incidental to preparing the property for occupancy, which in my opinion appear to be proper charges to this account; the charges to the Furniture and Equipment accounts represent proper additions to this account and the allowance for depreciation appears to be adequate; it is to be noted that no depreciation has been taken into account on the new equipment purchased for the new headquarters, inasmuch as these purchases occurred principally in November and December; no depreciation reserve has been set up on the new building, and the Executive Secretary has informed me that this problem is receiving the consideration of the Board of Regents; the footings and extensions of the inventory were verified; all ascertainable liabilities have been included in the balance sheet; all recorded receipts from dues, initiation fees, exhibits, advertising, sales of publications, etc., were properly deposited in bank and all disbursements, as indicated by the vouchers, cancelled checks and bank statements, were properly recorded in the books of account.

Very truly yours,

(Signed) H. I. MacLean,
Certified Public Accountant

AMERICAN COLLEGE OF PHYSICIANS, INC.

Balance Sheet, December 31, 1936

General Fund

Assets

Cash in banks and on hand		$ 21,656.56
Accounts Receivable:		
Advertising	$ 367.00	
Due from Broker	2,180.31	
American Board of Internal Medicine	4,697.00	7,244.31
Inventory of Keys, Pledges and Frames, at cost		169.40
Accrued Income on General Fund Investments		127.08
Accrued Income on Endowment Fund Investments		596.44
Investments at Book Value		22,631.03
Insurance Deposit		555.00
Deferred Expenses, 21st Annual Session		2,299.50
Deferred Claims:		
Banks in process of liquidation		
Bank of Pittsburgh	$1,461.97	
Exchange National Bank, Pittsburgh	1,749.20	
Highland National Bank, Pittsburgh	3,081.22	6,292.39
College Headquarters, Real Estate		57,343.70
Furniture and Equipment, at cost	8,452.40	
Less Allowance for Depreciation	2,862.98	5,589.42
		$124,504.83

Liabilities

Accounts Payable		$ 1,856.62
Deferred Income:		
Advance Collections for Exhibits, 21st Annual Session	$2,470.15	
Advance Subscriptions for Volumes XI and XII, ANNALS OF INTERNAL MEDICINE	345.16	2,815.31
General Fund, as annexed		119,832.90
		$124,504.83

Endowment Fund

Cash in banks		$ 1,337.09
Accrued Interest		596.44
Investments at Book Value		60,447.73
		$ 62,381.26
TOTAL ASSETS		$186,886.09

Endowment Fund, Principal	$ 61,784.82
Advance Account, Accrued Income due General Fund	596.44
	$ 62,381.26
TOTAL LIABILITIES	$186,886.09

General Fund

For the Year Ended December 31, 1936

Balance, January 1, 1936			$ 99,047.47
Less:			
Transfer to Endowment Fund of the Initiation Fees of Life Members, net			660.00
			$ 98,387.47
Summary of Operations for the Year ended December 31, 1936:			
Income:			
Annual Dues	$23,070.95		
Subscriptions, Annals of Internal Medicine	22,320.43		
Advertising, Annals of Internal Medicine	6,014.06		
Initiation Fees	11,455.00		
Income from Invested Funds (General)	2,358.02		
Income from Endowment Fund (net)	652.97		
Exhibits, 20th Annual Session	6,291.04		
Guest Fees, 20th Annual Session	297.00		
Other Income	297.75		
Profit on Investments of General Fund sold (net)	1,077.04	$73,834.26	
Expenses:			
Salaries	$18,629.69		
Postage, Telephone, Telegraph, etc.	3,064.22		
Office Supplies and Stationery	1,030.92		
Printing	17,345.05		
Traveling Expenses	4,213.96		
Rent and Maintenance	2,845.99		
College Headquarters:			
Maintenance	$ 609.82		
Taxes	486.20		
Insurance	232.37		
Miscellaneous	53.25	1,381.64	
Depreciation on Furniture and Equipment		393.10	
Other Expenses:			
20th Annual Session	$1,832.12		
Annals of Internal Medicine	212.95		
Miscellaneous	1,439.19	3,484.26	52,388.83
Net Income for the Year Ended December 31, 1936			21,445.43
Balance, December 31, 1936			$119,832.90

Endowment Fund

For the Year Ended December 31, 1936

Principal Account:			
Balance, January 1, 1936			$58,281.72
Add:			
Life Membership Fees received during 1936			2,425.00
Transfer of Initiation Fees of New Life Members from General Fund, net			660.00
Profit on Investments, sold and matured			418.10
Balance, December 31, 1936			$61,784.82
*Income Account:			
Income from Investments			$ 2,242.21
Less:			
Research Fellowship		$1,514.11	
John Phillips Memorial Prize		75.13	1,589.24
Balance, Credited to General Fund for the period			$ 652.97

* At December 31, 1936, the accrued income included in the Income from Investments of the Endowment Fund amounted to $596.44, and is due to the General Fund.

DETAILED STATEMENT OF OPERATIONS

For the Year Ended December 31, 1936

General Income:				
Annual Dues			$23,070.95	
Initiation Fees			11,455.00	
Income from Endowment Fund (Net, after deducting Research Fellowship stipend and John Phillips Award)			652.97	
Income from General Fund Investments			2,358.02	
Profit from Sales of Keys, Pledges and Frames			30.53	
Sales of 1935 Directory			13.30	
Profit on Investments of General Fund sold (Net)			1,077.04	
Dividend on Insurance Deposit			30.00	
Gift of Equipment			218.00	$38,905.81
Twentieth Annual Session:				
Expenses:				
Salaries		$ 3,782.54		
Communications (Postage, Telephone, etc.)		384.38		
Office Supplies and Stationery		148.76		
Printing		783.29		
Traveling Expenses		3,044.75		
Miscellaneous:				
Advertising	$ 67.62			
Badges	201.58			
Convocation and President's Reception	513.49			
Equipment Rental	100.00			
Ladies Committee	204.65			
Publicity and Reporting	196.00			
Smoker	398.03			
Other Miscellaneous Items	150.75	1,832.12	9,975.84	
Income:				
Exhibits (Net)		$ 6,291.04		
Guest Fees		297.00		
Profit on Banquet		5.92	6,593.96	
Net Expenses of Clinical Session			$ 3,381.88	
Annals of Internal Medicine:				
Income:				
Subscriptions:				
Volume I	$ 21.20			
Volume II	24.20			
Volume III	15.20			
Volume IV	20.48			
Volume V	16.80			
Volume VI	12.91			
Volume VII	24.91			
Volume VIII	81.70			
Volume IX	1,402.14			
Volume X	20,700.89	$22,320.43		
Advertising (Net):				
Volume IX	$ 2,917.97			
Volume X	3,096.09	6,014.06		
		$28,334.49		
Expenses:				
Salaries	$ 6,156.51			
Communications (Postage, Telephone, etc.)	1,055.54			
Office Supplies and Stationery	402.00			
Printing	15,840.54			
Miscellaneous	135.78			
Allowances, Adjustments and Purchases	77.17	23,667.54		
Net Profit on ANNALS OF INTERNAL MEDICINE				4,666.95
Total Income				$43,572.76
Forward			$ 3,381.88	$43,572.76

Brought Forward		$ 3,381.88	$43,572.76
Executive Secretary's Office:			
Expenses:			
Salaries	$ 8,690.64		
Communications (Postage, Telephone, etc.)	1,624.30		
Office Supplies and Stationery	480.16		
Printing	721.22		
Rent and Maintenance	2,845.99		
Traveling Expenses	1,169.21		
Fee to Custodian of Securities	130.17		
Loss on Foreign Exchange	8.75		
Miscellaneous Items	504.59	16,175.03	
New College Headquarters:			
Maintenance	$ 609.82		
Taxes	486.20		
Insurance	232.37		
Miscellaneous	53.25	1,381.64	
Investment Counsel Service		200.00	
ANNALS OF INTERNAL MEDICINE distributed Free to Life Members		390.00	
Depreciation on Furniture and Equipment		393.10	
Printing 1936 Supplement to 1935 Directory		205.68	22,127.33
Net Income for the Year Ended Dec. 31, 1936			$21,445.43

INVESTMENTS

December 31, 1936

Par Value	*Bonds*	*Endowment Fund Securities*	*General Fund Securities*	
$ 5,000	Bell Telephone of Canada, 5s, 1955	$ 5,562.50		
2,000	Canadian National (West Indies) SS. Co., Ltd., 5s, 1955	2,040.00		
4,000	Chesapeake and Ohio RR., Series "D," 3½s, 1996	4,060.00		
5,000	Cities Service Co., 5s, 1950		$ 4,075.90	
1,000	City of Montreal, 5s, 1956	1,071.30		
5,000	Commonwealth Edison Co., First, Series "F," 4s, 1981	4,744.35		
5,000	Government of the Dominion of Canada, 4s, 1960	4,662.50		
2,000	Great Northern Railway Co., Series "H," 4s, 1946	2,100.45		
5,000	New York Central RR., 3¾s, 1946	4,900.00		
5,000	Pennsylvania Railroad, Gen., 4¼s, Series "E," 1984		5,013.10	
2,000	Port of New York Authority, New York-New Jersey Interstate Bridge, 4½s, Series "B," 1952	2,042.20		
2,000	Port of New York Authority, New York-New Jersey Interstate Tunnel, 4¼s, Series "E," 1958	2,065.40		
5,000	Texas and Pacific Railway, Gen. and Ref., B, 5s, 1977	5,313.40		
2,000	U. S. Treasury, 4s, 1954	1,998.13		
20,000	U. S. Treasury, 3¼s, 1945	19,887.50		
$70,000	TOTALS, Bonds	$60,447.73	$ 9,089.00	$69,536.73
Shares	*Stocks*			
50	General Motors Corporation		$ 1,584.75	
45	Mid-Continent Petroleum Corporation		963.93	
70	National Breweries, Ltd.		2,803.50	
20	J. C. Penny Co.		1,375.30	
20	Standard Brands, Inc.		2,467.50	
50	Timken Roller Bearing Company		3,407.25	
20	Union Carbide and Carbon Corporation		939.80	
	TOTAL, Stocks		$13,542.03	
	TOTAL, Investments	$60,447.73	$22,631.03	$83,078.76

ANNALS OF INTERNAL MEDICINE

Cost Analysis

	Number of pages			
	Scientific matter	News notes, Covers, etc.	Paid advertising	Total
Volume I —July, 1927 to June, 1928	1040	151¼	10¾	1202
Volume II —July, 1928 to June, 1929	1195	254½	98½	1548
Volume III —July, 1929 to June, 1930	1133	248	163	1544
Volume IV —July, 1930 to June, 1931	1435	300	185	1920
Volume V —July, 1931 to June, 1932	1481	191	188	1860
Volume VI —July, 1932 to June, 1933	1582¾	171¼	186	1940
Volume VII —July, 1933 to June, 1934	1517	137½	195¾	1850
Volume VIII—July, 1934 to June, 1935	1597	149¼	193¾	1940
Volume IX —July, 1935 to June, 1936	1708	157	241	2106

Average Circulation: Volume I —1803
Volume II —1999
Volume III —2437
Volume IV —2722
Volume V —3090
Volume VI —3134
Volume VII —3173
Volume VIII—3388
Volume IX —3658 (Circulation, June, 1936, Issue—3,808)

ANNALS OF INTERNAL MEDICINE—Cost Analysis—*Continued*

	Volume VII (11-30-36)			Volume VIII (11-30-36)			Volume IX (11-30-36)		
Income:									
Subscriptions (Net)			$17,807.77			$19,428.61			$21,181.64
Advertising (Net)			4,717.84			4,691.70			5,540.54
			$22,525.61			$24,120.31			$26,722.18
Expenditures:									
Salaries			$ 5,078.11			$ 5,090.21			$ 5,998.35
Communications (Postage, etc.)			940.48			825.04			1,019.48
Office Supplies and Stationery			487.98			449.33			229.88
Printing		$11,931.41			$13,950.37			$14,959.28	
Less Repayment for Excess Illustrations	$ 90.15			$152.44			$ 74.67		
Less Inventory of Stock	*100.00	190.15	11,741.26	*100.00	252.44	13,697.93	*200.00	274.67	14,684.61
Traveling Expenses			13.17			6.15			
Miscellaneous (Editor's Office, Copyright, etc.)			218.61			138.37			133.22
			$18,479.61			$20,207.03			$22,065.54
Surplus—Vol. VII			4,046.00	Surplus—Vol. VIII		3,913.28	Surplus—Vol. IX		4,656.64
			$22,525.61			$24,120.31			$26,722.18

* An arbitrary valuation determined from estimation of future sale value, and not on actual cost of printing.

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